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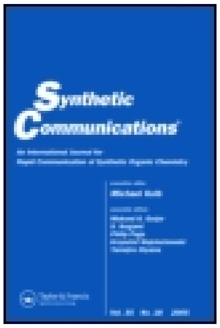

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Application of Hantzsch Dihydropyridine in Copper-Catalyzed [3+2] Cycloaddition of Terminal Alkynes with Azides

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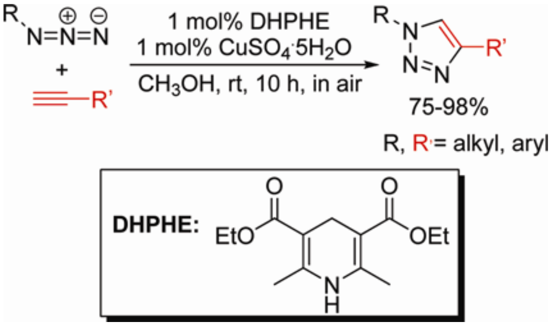
Abstract

2,6-Dimethyl-3,5-bis(ethoxycarbonyl)-1,4-dihydropyridine (dihydropyridine Hantzsch ester, DHPHE) and $CuSO_4·5H_2O$ efficiently accelerated azide-alkyne cycloaddition reactions of both aliphatic and aromatic substrates and gave 1,4-disubstituted 1,2,3-triazoles as the only isomer in good to excellent yields at room temperature with 1 mol% of $CuSO_4·5H_2O$/DHPHE (1:1 in molar ratio). The reaction could be carried out smoothly in methanol in air with high efficiency. DHPHE may play multiple important roles in the reaction: a reducing reagent to generate the catalytic center copper(I) from $CuSO_4$, a base to help form the intermediate acetylide and a ligand to stabilize the catalytic copper (I) species via coordination after being transformed to pyridine derivative.

[Supplementary materials are available for this article. Go to the publisher's online edition of *Synthetic Communications*® for the following free supplemental resource(s): Full experimental and spectral details.]



KEYWORDS: Hantzsch ester; dihydropyridine; click chemistry; cycloaddition; copper

INTRODUCTION

Since Cu(I)-catalyzed azide-alkyne cycloaddition (AAC) for regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles was reported,[1] a number of papers have appeared to develop this simple "click" methodology[2,3] and disclose its applications in such fields as materials science[4] and medicinal chemistry[5] due to their unique chemical and structural properties.[6] Typically, such a cycloaddition reaction involves an intermediate of Cu(I) acetylide, which then participates in an annulation with an azide upon coordination. Mostly the copper sources came from direct addition of Cu(II) species, from which catalytic Cu(I) could be generated in situ in the presence of a reducing agent such as sodium ascorbate (NaAsc).[7] Cu(I) salts have rarely been used directly because of instability[8] and the formation of coupling byproducts.[9] To keep the catalyst effective and reactive, Cu(I)-catalyzed AAC usually required the presence of a nitrogen-containing base (for Cu^I salts), exclusion of oxygen from the reaction system,[10] and sometimes high loading of catalyst that might be a severe obstacle when it was applied in large scales.[11]

Recently, some AAC catalytic systems have been developed, for example, Cu(I) species immobilized on solid supports,[12] copper-containing nanoparticles,[13] and amine, phosphane or carbene-based complexes,[14] to enhance catalytic activity and/or recycle the catalysts. With reducing agent free, chelation-assisted Cu(II)-accelerated AAC was reported on picolyl substrates,[15] it was proposed that the alcoholic solvents and/or terminal alkynes helped form Cu(I) species.

2,6-Dimethyl-3,5-bis(ethoxycarbonyl)-1,4-dihydropyridine (dihydropyridine Hantzsch ester, DHPHE), readily available by simple preparation[16] or commercial sources, stable in air, soluble in most organic solvents, and always used as a model compound for Coenzyme I, NADH, can reduce Cu(II) to Cu(I) to give pyridine Hantzsch ester (PHE),[17] which may serve as both a ligand[18] and a base. Bearing this in mind, DHPHE should take multiple roles such as a reducing reagent to form copper(I), a base to help form Cu(I) acetylide and a ligand for Cu(I) species after oxidized by copper(II), thus may find application in AAC as an alternative to NaAsc when it is carried out in organic media. Herein we report the results of this efficient catalytic system, $CuSO_4$/DHPHE, for AAC in air at room temperature.

DISCUSSION

Simple substrates such as benzyl azide and phenylacetylene were chosen for the model reaction, the catalytic activity of copper(I) depended on the counterions: with 1 mol% loading of Cu^{2+} and DHPHE, $CuSO_4{\cdot}5H_2O$ gave the highest yield and exhibited high catalytic activity in MeOH: 98% yield in 10 h, whereas other Cu(II) salts such as $CuCl_2{\cdot}2H_2O$ (20%), $Cu(NO_3)_2{\cdot}3H_2O$ (40%), $Cu(AcO)_2{\cdot}H_2O$ (48%), $Cu(ClO_4)_2{\cdot}6H_2O$ (12%) gave poor to moderate yields; in the absence of DHPHE and PHE, CuBr (10%)

and CuI (6%) gave poor yields. Increasing the catalyst loading enhanced the efficiency of the reaction, for example, with the loadings changed to 10 mol%, both $CuSO_4{\cdot}5H_2O$/DHPHE (96% in 4 h) and CuBr/PHE (90% in 10 h) gave excellent yields. Lowering the loading of $CuSO_4{\cdot}5H_2O$ even to 0.25 mol% had a little effect on the yield (93% in 24 h). Addition of 5 mol% $CaCO_3$ as acid scavenger had little improvement on the yield (98%), though protons, which may prevent the formation of Cu (I) acetylide, might be produced during the aromatization of DHPHE. [17]

DHPHE is necessary for the reaction with the ability of reducing to generate copper(I) species. With 1 mol% $CuSO_4{\cdot}5H_2O$, 19% yield of the above model reaction was achieved in the absence of DHPHE even though the reaction was extended to 24 h, which was in sharp contrast with that in the presence of DHPHE (98% yield). On the other hand, the presence of PHE (1 mol%), the product of DHPHE upon oxidation, improved the yields of the reactions with copper(I) halides and $CuSO_4{\cdot}5H_2O$ (the yields were 25%, 15% and 36% for 1 mol% CuBr, CuI and $CuSO_4{\cdot}5H_2O$, respectively, whereas the yields were 10% , 6% and 19% without PHE as mentioned above) , which indicates that PHE may play dual roles of ligand and base in the reaction and improve the catalytic activity.

Besides in MeOH, in DMF it also gave excellent yield (98%), solvents such as EtOH (70%), DMSO (60%), H_2O (60%) were moderate, while t-BuOH, i-PrOH, THF, CH_3CN

were poor (less than 10%). However, in DMF, the reaction was required to be carried out in an inert atmosphere.

We performed AAC under the optimized conditions as follows: 1 mol% $CuSO_4 \cdot 5H_2O$ as the catalyst, 1 mol% DHPHE as the additive, and methanol as the reaction medium, at room temperature without the air excluded out.

As shown in Table 1, for all the examined substrates, reactions were run smoothly to reach completion in about 10 h, and the corresponding triazoles were obtained in high yields and quality after simple filtration and washings. Several single crystals suitable for X-ray diffraction were obtained by slow diffusion of petroleum ether into each CH_2Cl_2 solution of the products **3, 4, 18**. The configurations confirmed the structure as the 1,4-isomer. Figure 1 shows the structure of **18**.

Electronic properties of the substituents seem to take little effect: both electron-rich and electron-poor substrates reacted well even with steric hindrance as shown in Entries 4, 11, 12, 16, 18. Double "clicks" also worked well with diynes and diazides as shown in Entries 19-23. This is probably due to the unique nature of the catalytic system $CuSO_4 \cdot 5H_2O$/DHPHE: DHPHE may take multiple roles such as a reducing reagent to form copper(I), a base to help form Cu(I) acetylide and a ligand for Cu(I) species after oxidized by copper(II). It should be noted that the solubility of the substrates in methanol was vital for the reaction rate. For those solid substrates that were not readily soluble in methanol, some CH_2Cl_2 (10% in volume) was used to facilitate dissolving, and the reactions could complete without time prolonged and gave excellent yields.

In conclusion, we have developed a new catalytic system, $CuSO_4{\cdot}5H_2O$/DHPHE, which can highly efficiently promote the [3+2] cycloaddition of both aliphatic and aromatic azides and alkynes in methanol without exclusion of air at room temperature. Electronic properties and steric hindrance of the substituents on the substrates take little effect on the reaction efficiency. DHPHE may take multiple roles in the reaction, such as a reducing reagent to form copper(I), a base to help form Cu(I) acetylide and a ligand for stabilizing Cu(I) species after oxidized by copper(II). Moreover, a single regioisomer, 1,4-disubstituted 1,2,3-triazole formed. This system may find applications especially for those AAC reactions in which substrates are only soluble in organic solvents.

EXPERIMENTAL

General Procedure For Cycloaddition Of Alkyne-Azide

To a mixture of azide (0.79 mmol) and alkyne (0.83 mmol) was added a solution of $CuSO_4{\cdot}5H_2O$ (10 µL, 2 mg, 1 mol% based on azide, with 2.00 g of $CuSO_4{\cdot}5H_2O$ in 10 mL H_2O), followed by a solution of dihydropyridine Hantzsch ester (10 µL, 2.2 mg, 1 mol% based on azide, with 2.20 g of dihydropyridine in 10 mL CH_3OH), and finally methanol (1 mL) via syringes. The mixture was stirred for a period as indicated at room temperature. After checked by TLC ($CHCl_3/CH_3OH$), the reaction mixture was concentrated to dryness under reduced pressure. A small amount of water was used to wash the solid product followed by petroleum ether (^{1}H NMR spectrum showed it is pure). If needed, the reaction mixture was loaded onto a short plug of silica gel using a fine solvent gradient ($CHCl_3/CH_3OH$) to afford the analytically pure product. For some substrates, the scales were reduced.

2-((1-Butyl-1*H*-1,2,3-Triazol-4-Yl)Methyl)Isoindoline-1,3-Dione (Compound 18)

White solids. Yield: 100 mg, 76% (Table 1, Entry 18). mp: 125-127 ^{o}C ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm 7.86 (d, J=3.0 Hz, 2H), 7.73 (d, J=3.3 Hz, 2H), 7.59 (s, 1H), 5.00 (s, 2H), 4.31 (dd, J_1=7.5 Hz, J_2=7.2 Hz, 2H), 1.91-1.81 (m, 2H), 1.38-1.26 (m, 2H), 0.94 (dd, J_1=7.2 Hz, J_2=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm 168.1, 143.0, 134.5, 132.3, 123.8, 123.0, 50.4, 33.4, 32.6, 20.0, 13.8. GC-MS (EI, m/z): 284 (M^+, 100). Elem. Anal.: Calcd. for $C_{15}H_{16}N_4O_2$: C, 63.37; H, 5.67; N, 19.71. Found: C, 63.32; H, 5.48; N, 19.90%.

SUPPLEMENTARY DATA

Full experimental detail, characterization data (including melting points, copies of ^{1}H and ^{13}C NMR spectra, GC-MS and/or elemental analysis), crystallographic structure parameters and X-ray crystallographic information files (CIFs) for compound **3**, **4** and **18** (CCDC 802897-802899), and X-ray molecular structures of **3** and **4** are available online.

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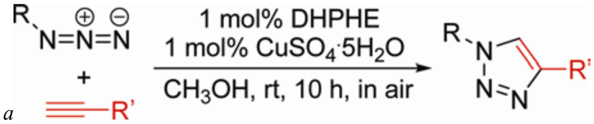
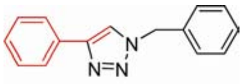
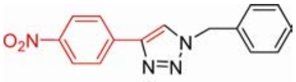
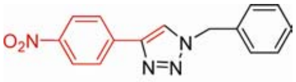
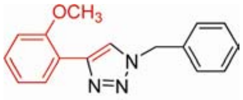
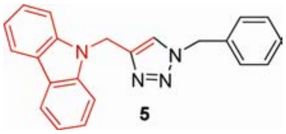
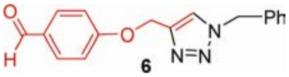
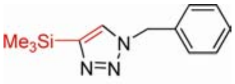
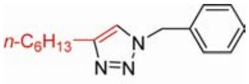
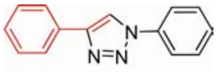
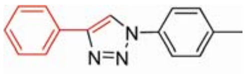
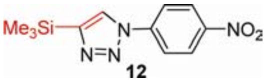
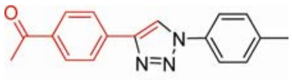
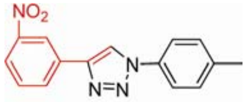
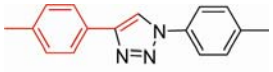
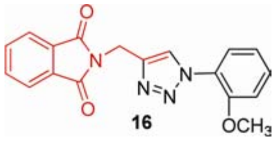
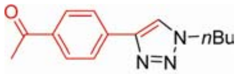
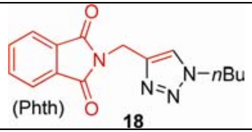
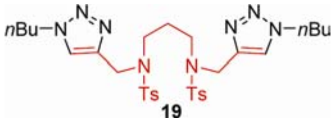
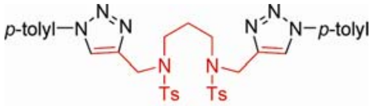
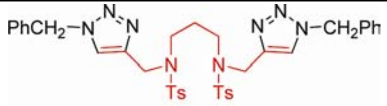
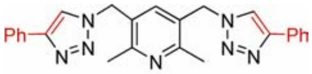
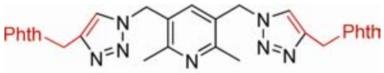


Table 1. Scope of substrates.[a]

Entry	Product	Yield (%)[b]
1	 **1**	98
2	 **2**	91
3	 **2**	90
4	 **4**	97
5	 **5**	87
6	 **6**	80[d]
7	 **7**	92[c]
8	 **8**	86[c]
9	 **9**	75[e]
10	 **10**	89
11	 **11**	90
12	 **12**	91[d]

13	 **13**	90
14	 **14**	93
15	 **15**	84
16	 **16**	$92^{c,d}$
17	 **17**	85
18	 **18**	76^{d}
19	 **19**	91
20	 **20**	90
21	 **21**	95
22	 **22**	93
23	 **23**	96^{d}

[a] Reaction conditions: azide (1.0 equiv), alkyne (1.05 equiv), CH_3OH, 1 mol% $CuSO_4 \cdot 5H_2O$ (in 8 mM), 1 mol% DHPHE, 10 h, r.t., exposed in air.

[b] Isolated yield.

[c] Completed in 12 h.

[d] Substrate was dissolved in 0.1 mL CH_2Cl_2 and then the other reactants were added .

[e] Reaction time was prolonged to 14 h.

Figure 1. The single-crystal structure of triazole **18**.