Multicomponent catalytic synthesis of 1,2,3-triazoles by regio specific copper(I)-catalyzed 1,3-dipolar cycloadditions of terminal alkynes to azides

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ABSTRACT

An efficient, facile, and practical liquid-phase combinatorial synthesis of various 1,2,3-triazoles was synthesizedfrom phenylacetylene, sodium azide and alkyl halide via a one-step process in the presence of a catalytic amount of a copper-salen complex in the water.   © 2015 Trade Science Inc. - INDIA

INTRODUCTION

1,2,3-Triazoles are important five-membered nitrogen heterocycles, involved in a extensive range of industrial applications such as agrochemicals, optical brighteners dyes, corrosion inhibitions (of copper and copper alloys), and biologically active agents[1]. Earlier, the compounds were in general prepared by the coupling of alkynes and azides to form a mixture of 1,4-substituted- and 1,5-substituted-1,2, 3-triazoles at high temperature[2]. The recent important investigations lead to the click chemistry approach[3]. The Huisgen 1,3-dipolar cycloaddition[4] of azides and alkynes resulting in 1,2,3-triazoles is one of the most powerful click reactions.

Since the discovery of the Cu(I)-catalyzed azide alkynecycloaddition (CuAAC),[5] the number of its applications indifferent fields of chemistry has exploded. The reaction hasenabled discovery of novel bioactive compounds, ligands fortransition metals, new materials, and bioconjugates, under-scoring its exceptionally broad scope and fidelity[6].

Several members of the 1,2,3-triazole family have indeed shown interesting biological properties, such as anti-allergic,[7] anti-bacterial,[8] and anti-HIV activity[9]. Additionally, 1,2,3-triazoles are found in herbicides, fungicides, and dyes[10]. The recently discovered copper(I) catalysis of this transformation,[11] which accelerates the reaction up to 10^7 times, has placed it in a class of its own and has enabled many novel applications[12].

Multicomponent reactions are the important class of organic synthesis that involves transformation of various reactants into the desire product in a single step. The multicomponent reaction of alkynes and azides formed in situ from alkyl halides and sodium azide yielding. 1,2,3-triazoles is a powerful one pot three component click reaction.

The Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC),[13] one of the most reliable "click reactions",[14] has enabled the practical and efficient preparation of 1,4-disubstituted-1,2,3-triazoles, from a wide range of substrates with excellent selectivity, which cannot be prepared via traditional Huisgen uncatalyzed thermal approaches[15]. Active copper(I) catalytic species can be prepared in situ by reduc-

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tion of copper(II) salts, oxidation of copper(0) metal,[16] or copper(II)/copper(0) comproportionation[17].

RESULTS AND DISCUSSION

Using metal-salen complexes for the synthesis of 1,4-substituted-1,2,3-triazoles

Metal-salen complexes have been recognized as beingamong the most promising catalysts for various reactions. These complexes show wide applicability, and are now used as catalysts for a variety of enantioselective reactions, such as oxidation,[18, 19] the Diels–Alder reaction,[20] the addition of TMSCN to aldehydes,[21] and the conversion of 1,2-epoxyethanes to 2-haloethanols with molecular halogen[22].

In conjunction with ongoing work in our laboratory on the synthesis and formation of metal-salen complexes with different molecules[22], and we found that these complexes efficiently catalyzed the condensation reaction of phenylacetylene with different alkyl halideand sodium azideto form 1,2,3-triazoles in water (Scheme 1).

In this study, the preparation of 1,2,3-triazoles from phenylacetylene and alkyl halide in the pres-
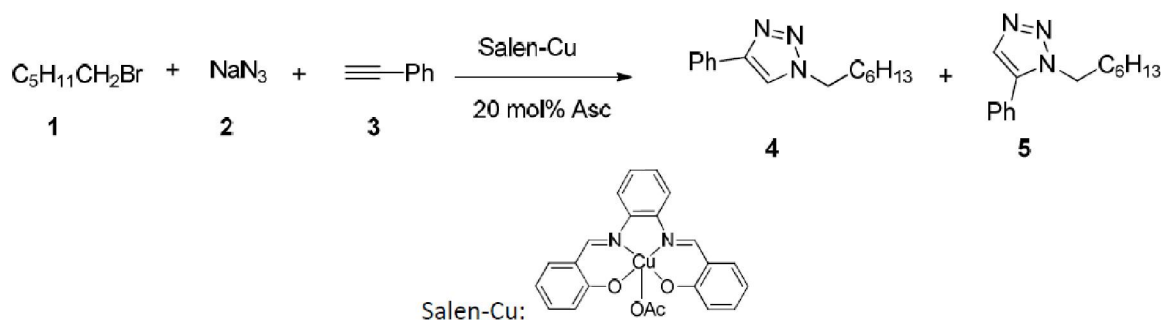
Scheme 1

TABLE 1 : The reaction of phenylacetylene (1.0 mmol) with alkyl halide (1.0 mmol) and sodium azide (1.2 mmol) in the precene of ascorbic acid (20mol%) using copper (II)catalyst (10 mol%) in different solvent

Entry	Catalyst (10 mol%)	solvent	Temperature °C	Time[h]	Yield4[a] [%]
1	-	Ethanol	reflux	12	-
2	Cu(salen)	Ethanol	Reflux	12	<10
3	Cu(OAc)2	Ethanol	Reflux	12	5
4	CuCl2	Ethanol	Reflux	12	-
5	Cu(salen)	DMSO	70	45 min	85
6	Cu(salen)	THF	reflux	12	20
7	Cu(salen)	DMF	100	10	10
8	Cu(salen)	H_2O	reflux	10	<10
9	Cu(salen)	Chloroform	Reflux	10	<5
10	Cu(salen)	AcOEt	Reflux	10	-
11	Cu(salen)	Acetonitril	Reflux	10	10
12	salen	DMSO	Reflux	10	-
13	Cu(salen)	--	-	10	<5
14	Cu(salen) (5 mol%)	DMSO	70	1	50
15	Cu(salen) (20 mol%)	DMSO	70	45 min	85
16	Cu(salen)	DMSO	60	45 min	85
17	Cu(salen)	DMSO	30	45 min	68
18	Cu(salen)	DMSO	20	45 min	45

a) Isolated yield
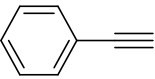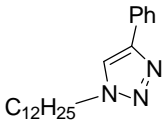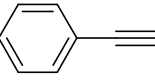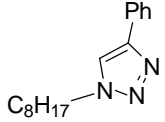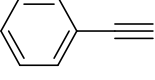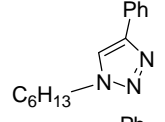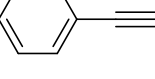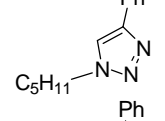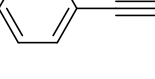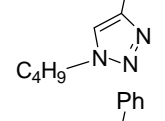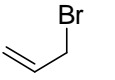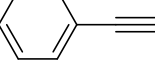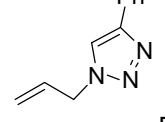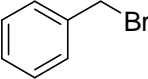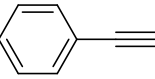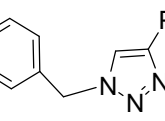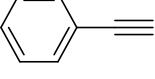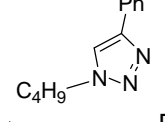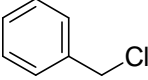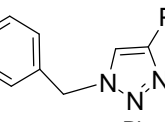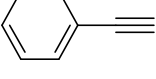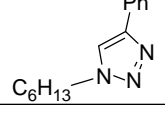
ence of a catalytic amount of copper-salen complex was examined. In a general procedure, to a mixture phenylacetylene, sodium azide and alkyl halide in water was amount of the catalyst in water and the mixture was stirred at 80ºC. While the reaction of phenylacetylene, sodium azide and alkyl halide in the absence of the catalyst (TABLE 1, entry 1) or absence of the metal in the salen structure (TABLE 1, entry 13) showed that no reaction occurred.

According to TABLE 1, the best results were obtained with the use of 10 mol% of copper-salen.

When the amount of the catalyst was reduced, the yield of the products decreased, whereas raising the catalyst concentration did not lead to an appreciable increase of the yield and a shorter reaction time.

The effect of solvents on the condensation reaction utilizing copper-salen complex was also investigated as shown in TABLE 1. We found that these reactions appeared to be largely dependent on the nature of the solvent. Obviously, DMSO stands out as the solvent of choice with its fast reaction rate, high yield, selectivity, cheapness acceptability.

TABLE 2 : Reaction of phenyleacetylene (1.0 mmol) with alkyl halide (1.0 mmol) using Cu(II)-salen complex under optimized condition

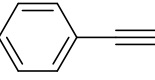| Entry	Alkyl Halide	Alkyne	Product	Time/h	Yield(%)
1	$C_{11}H_{23}CH_2Br$	phenylacetylene	triazole, $C_{12}H_{25}$, Ph	1	70
2	$C_7H_{15}CH_2Br$	phenylacetylene	triazole, C_8H_{17}, Ph	2	80
3	$C_5H_{11}CH_2Br$	phenylacetylene	triazole, C_6H_{13}, Ph	3	85
4	$C_4H_9CH_2Br$	phenylacetylene	triazole, C_5H_{11}, Ph	8.5	97
5	$C_3H_7CH_2Br$	phenylacetylene	triazole, C_4H_9, Ph	2	65
6	allyl bromide	phenylacetylene	triazole, allyl, Ph	1.5	90
7	benzyl bromide	phenylacetylene	triazole, benzyl, Ph	0.5	85
8	$C_3H_7CH_2Cl$	phenylacetylene	triazole, C_4H_9, Ph	3.5	80
9	benzyl chloride	phenylacetylene	triazole, benzyl, Ph	3	96
10	$C_5H_{11}CH_2I$	phenylacetylene	triazole, C_6H_{13}, Ph	2	70

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Scheme 2

Homogeneous Catalytic Benzimidazole Synthesis- and 1,5-substituted-1,2, 3-triazoles

Finally, using the optimized conditions, the reaction of phenyleacetylene (1 mmol) and alkyl aldehydes (1mmol) were carried out in the presence of homogeneous catalysts at room temperature to give the corresponding 1,2,3-triazoles in high yields. Under optimized reaction conditions, we obtained exclusively 1,4-substituted 1,2, 3-triazoles4products and no 1,5-substituted-1,2, 3-triazoles 5 were observed (Scheme 1). We studied the reaction of the phenyleacetylene for rteaction with alkyl halideand sodium azide under the optimized conditions and the results are shown in TABLE 2. In all cases, the reaction was clean and carried out within 30 min to 8 h. All products were characterized by IR, ¹H NMR, ¹³C NMR and mass spectrometry.

In a typical run, phenyleacetylene (1 mmol), alkyl halide (1 mmol) and Cu(salen) (10 mol%) were allowed to react in DMSO at 70ºC for 30 min. As shown, active alkyl halides such as benzyl chloride and allyl bromide afforded the desired 1,2,3-triazol in excellent yields (TABLE 2).

Mechanistically, we believe that the formation of 1,2,3-triazols under these conditions follows through the known intermediate schiffs bases A, which exist in equilibrium with the metal cyclic intermediate (Scheme 2).

CONCLUSIONS

In summary, we have developed a general and efficient one-pot synthetic route to 1,2,3-triazoles from phenylacetylene and alkyl halide using a copper (II)-salen complex. The mild reaction conditions, the fast reaction times, large scale synthesis, easy and quick isolation of products, and excellent yields are the main advantages of this procedure which make it an attractive and useful contribution to the present methodologies. Hence, we believe that it will find wide application in organic synthesis as well as in industry.

Experimental section

Chemicalmaterials were either prepared in our laboratories or were purchased from Fluka, Aldrich,or Merck. The purity determination of the substrates and reaction monitoring were accomplished by TLC (silica gel PolyGram SILG/UV254 plates). Column chromatography (CC): short glass columns of silica gel 60 (SiO$_2$; 70–230 mesh); 15–30 g of SiO$_2$ for 1 g of crude mixture. M.p: open capillary; Büchi-535 circulating-oil melting-point apparatus. IR Spectra: Shimadzu-FT-IR 8300 spectrophotometer; in cm⁻¹. NMR Spectra: Bruker-Avance-DPX-250 (¹H at 250 and ¹³Cat62.9 MHz) in pure deuterated solvents withMe$_4$Si as internal standard; d in ppm, J inHz.MS:

General procedure

The Cu(salen) catalyst was subjected to successive reuses under the reaction conditions: For each reaction, alkyl halide (1 mmol), alkyne (1 mmol), ascorbic acid and sodium azide (1.2 mmol) were heated in DMSO (2 mL) in the presence of the catalyst (10 mol%,) at 70°C in auncapped vial. The reaction was complete after appropriate time (TABLE 2) as monitored by TLC analysis. After the reaction was complete the whole reaction mixture was poured in water and the precipitate was collected by filtration. After filtering, the products purified by column chromatography using mixture of n-hexane and ethyl acetate as elute.

1-octyl-4-phenyl-1H-1,2,3-triazole[13]. White solid: mp 74-75 °C. 99 % yield.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.78 (d, J= 7.2 Hz, 2H), 7.73 (s, 1H), 7.36 (t, J= 7.2 Hz, 2H), 7.27 (t, J= 7.2 Hz, 1H), 4.32 (t, J= 7.2 Hz, 2H), 1.87 (br s, 2H), 1.20-1.27 (m, 10H), 0.82 (t, J= 3.2 Hz, 3H)

^{13}C NMR (100.59 MHz, CDCl$_3$): δ 147.7, 130.9, 128.9, 128.1, 125.7, 119.7, 50.5, 31.8, 30.4, 29.1, 29.0, 26.6, 22.7, 14.2.

1-benzyl-4-phenyl-1H-1,2,3-triazole white solid (yield 96%). mp: 128-130 C.

^{1}H NMR (400 MHz, CDCl$_3$): δ H 7.79(t, J=4.4 Hz, 2H), 7.66(s, 1H), 7.34-7.40(m, 5H), 7.25-7.31(m, 3H), 5.54(s, 2H).

^{13}C NMR (100.59 MHz, CDCl$_3$): 148.15, 134.67, 130.52, 129.08, 128.74, 128.70, 128.09, 127.99, 125.65, 119.48, 54.15

1-pentyl-4-phenyl-1H-1,2,3-triazole[11]: white solid (yield 94%). mp: 70-71 C.

IR (KBr/cm^{-1}): 3734.40, 3118.35, 2924.67, 1461.53, 1214.21, 1076.02, 839.23, 759.57, 693.33, 521.80.

^{1}H NMR (400 MHz, CDCl$_3$): δH 7.84(t, J=4.2 Hz, 2H), 7.75(s, 1H), 7.41(t, J=7.6 Hz, 2H), 7.27 - 7.34(m, 1H), 4.36(t, J=7.2 Hz, 2H), 1.89-1.96(m, 2H), 1.30-1.37(m, 4H), 0.89(t, J=6. 8 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δC 147.56, 130.65, 128.71, 127.94, 125.56, 119.38, 50.29, 29.93, 28.48, 21.99, 13.74.

1-octyl-4-phenyl-1H-1,2,3-triazole[11]: white solid (yield 99%). mp: 68-70 C.

^{1}H NMR (400 MHz, CDCl$_3$): δH 7.83(d, J=7.2 Hz, 2H), 7.75(s,1H), 7.41(t, J=7.6 Hz, 2H), 7.31(t, J=7.4 Hz, 1H), 4.36(t, J=7.2 Hz, 2H), 1.92(t, J=7.0 Hz, 2H), 1.25-1.32(m, 10H), 0.87(t, J=6.8 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): 147.53, 130.66, 128.69, 127.91, 125.54, 119.37, 50.29, 31.58, 30.22, 28.92, 28.85,26.37, 22.47, 13.94.

1-dodecyl-4-phenyl-1H-1,2,3-triazole[11]: white solid(yield 90%). mp: 90-92 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ H 7.83(d, J=7.2 Hz, 2H),7.74(s, 1H), 7.42(t, J=7.6 Hz, 2H), 7.32(t, J=7.4 Hz, 1H), 4.38(t, J=7.2 Hz, 2H), 1.90-1.97(m, 2H), 1.25-1.34(m, 18H), 0.88(t, J=6.8 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$):147.70, 130.76, 128.78, 128.02, 125.67, 119.33, 50.40, 31.86, 30.32, 29.66, 29.56, 29.47, 29.35, 29.28, 28.98, 26.48, 22.64, 14.06.

1-benzyl-4-phenyl-1H-1,2,3-triazole[13]: White solid: mp 128-130 °C. yield= 91 %.

^{1}H NMR(400 MHz, CDCl$_3$): δ 7.80 (d, J= 7.2 Hz, 2H), 7.66 (s, 1H), 7.32-7.42 (m, 8H), 5.58 (s(400 MHz, CDCl3): δ 7.80 (d, J= 7.2 Hz, 2H), 7.66 (s, 1H), 7.32-7.42 (m, 8H), 5.58 (s2H);

^{13}C NMR (100.59 MHz, CDCl$_3$): δ 148.0, 135.0, 130.7, 129.1, 128.9, 128.7, 128.2128.1, 125.7, 120.1, 41.0.

1-benzyl-4-phenyl-1,2,3-triazole

^{1}H NMR (acetone-*d6*, 298 K): δ = 8.37 (s, 1H, triazole-H), 7.90 (ps d, 2H, 4-phenylHortho), 7.45-7.26 (m, 8H, ArH), 5.68 (s, 2H, CH2) ppm;

^{13}C NMR (acetone-*d6*, 298 K): δ = 148.2, 137.0, 132.2, 129.7, 129.6, 129.1, 128.8, 128.6, 126.2, 121.5, 54.3ppm

1-Allyl-4-phenyl-1H-1,2,3-triazole[5]:yield= 83%;

IR (neat): n= 698 (s), 764 (s), 933 (w), 991 (w), 1045 (w), 1076 (w), 1443 (m),1608 (w), 1720 (m), 2928 (m), 3074 (w) cm ;

^{1}H NMR (CDCl$_3$, 250 MHz): d= 4.96 (d, 2H, J= 6.1 Hz), 5.29 (dd, 2H, J =16.9, J =10.2 Hz), 5.86–6.08 (m, 1H), 7.23–7.42 (m,3H), 7.69 (s, 1H), 7.76 (dd, 2H, J =8.5, J = 1.1 Hz) ;

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^{13}C NMR (CDCl$_3$, 62.9 MHz): d=52.8, 118.7, 119.4, 120.2,125.7, 128.2, 128.8, 129.0, 129.5, 131.3.

1-Benzyl-4-phenyl-1H-1,2,3-triazole[5]: 91% yield ; mp 129–129.5 8C ;

IR (KBr/cm^{-1}): n= 694 (s), 729 (s), 768 (s), 1049 (m), 1076 (m), 1223 (m), 1358 (w), 1466 1 1 (m), 3121 (w) ;

^{1}H NMR (CDCl$_3$, 250 MHz): d=5.53 (s, 2H), 7.26–7.41 (m, 6H), 7.69 (s, 1H), 7.79–7.82 (m, 4H) ^{13}C NMR (CDCl$_3$, 62.9 MHz): d=54.1, 119.7, 125.7, 128.0,128.2, 128.7, 128.8, 129.1, 130.6, 134.7, 148.1; MS : m/z (%)= 237 (M + 2, 0.2), 236 (M +1, 7.3), 235 (M, 7.7), 207 (24.7), 206 (30.8), 179 (9.7), 149 (23.1), 116 (94.8), 91 (100), 57 (56.0) ; anal. calcd. for C H N (235.284): C 76.57, H 15 13 3 5.57: found : C 76.40, H 5.69. H

ACKNOWLEDGEMENTS

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