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Environmentally Benign Lewis Acid Promoted [2+3]-Dipolar Cycloaddition Reactions of Nitrile Imines with Alkenes in Water

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Abstract

Mild and environmentally benign Lewis acid promoted 1,3-dipolar cycloaddition reactions of α -hydrazonyl chlorides with alkenes in water are reported. These α -hydrazonyl chlorides, in the presence of Lewis acids, generate nitrile imines *in situ* which react with dipolarophiles to furnish the corresponding cycloaddition products. In many cases, the required times for the completion of the Lewis acid promoted 1,3-dipolar cycloaddition reactions in water were comparable to the equivalent reactions performed in an organic solvent. Analogous tetrahexylammonium chloride promoted 1,3-dipolar cycloaddition reactions were also performed. The comparison of reaction times and cycloadduct yields for the aforementioned 1,3-dipolar reactions in aqueous and organic media as well as the proposed role of the Lewis acid in the 1,3-dipolar cycloaddition reaction are described.

Keywords

Green Chemistry; Lewis Acids; 1,3-Dipolar Cycloadditions; Spiro-pyrazolines; Nitrogen heterocycles; Surfactants; Spiro heterocycles

Introduction

The 12 principles of green chemistry^[1–3] represent important guidelines in the design and development of processes to reduce and eliminate the use and generation of hazardous waste. The promotion of chemical reactions through catalysis significantly contributes^[1d–f] to the development of alternative reaction conditions by allowing the replacement of organic solvents with inexpensive, safe, and nontoxic solvents such as water.^[1e–j] Although water has typically been regarded as an uncommon reaction medium by many organic chemists, water is becoming an increasingly popular medium for organic reactions.^[1e,h–n,3,4] Of the chemists who make use of water as a solvent, many are often confronted with practical problems such as the antagonistic nature of water toward nucleophilic organic compounds and limited solubility of the organic components. However some chemists have taken advantage of the latter phenomenon.^{1e,1l,4e,5d,5f–g} Water is the most abundant solvent on

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Supporting Information (see footnote on the first page of this article): Characterization data and copies of the ¹H NMR and ¹³C NMR spectra.

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earth and is inexpensive, non-hazardous, non-toxic,^[1m-o,5] and environmentally benign from the green chemistry point of view.^[1d,e,m-o] In spite of the fact that Lewis acids have historically been important in promoting organic reactions,^[6,7] the vast majority of organic reactions are usually performed under anhydrous conditions because many Lewis acids quickly decompose in the presence of water.^[7a]

While a few Lewis acid promoted 1,3-dipolar cycloaddition reactions^[8,9] have been successfully employed in aqueous media where the Lewis acid was composed of silver^[10] or lithium,^[11] other aqueous based 1,3-dipolar cycloaddition reactions utilized prefabricated 1,3-dipoles.^[12] Furthermore, in some cases where 1,3-dipoles were generated in situ, micellar catalysts were often used under basic reaction conditions.^[13] A number of pharmaceutical drugs such as celecoxib^[14,15] and rimonabant^[16] feature the pyrazole moiety^[17] as the core pharmacophore, and structurally similar synthetic analogs such as pyrazolines and spiro-pyrazolines also have the potential to be biologically active. Due to the fact that 1,3-dipolar cycloaddition is commonly utilized for the syntheses of the aforementioned heterocycles,^[18] we are reporting the results from the investigation of a mild and environmentally friendly nitrile imine based 1,3-dipolar cycloaddition methodology toward pyrazoles, pyrazolines, and spiro-pyrazolines that utilize Lewis acids as reaction promoters in an aqueous environment at room temperature.

Previous investigations for the syntheses of 1,3,5-trisubstituted pyrazoles and spiro-pyrazolines in an organic solvent were reported.^[19] As an extension of the aforementioned study, the feasibility of Lewis acid promoted nitrile imine cycloadditions with various dipolarophiles were explored in water. The Lewis acid promoted reaction of the nitrile imine **2** or **5**^[20,21] with 2-methylene-1,3,3-trimethylindoline (**1**) respectively formed either pyrazole (**4**) or spiro-pyrazoline (**6**) in water (Scheme 1). The formation of a trisubstituted pyrazole and a spiro-pyrazoline from these cycloaddition reactions are in accordance with earlier reports.^[19] On the basis of these results, we decided to investigate and extend the application of this green methodology toward the synthesis of pyrazoles, spiro-pyrazolines, and pyrazolines.

Results and Discussion

Two electronically unique α -chlorohydrazones (unsubstituted **2**, and 4-methoxy **5**) were synthesized^[19] in order to determine if the electron density of the aromatic ring would affect the time of reaction completion, isolated yields and regioselectivity of the 1,3-dipolar cycloadditions. The indoline dipolarophile **1** reacted with aryl hydrazonyl chlorides **2** or **5** in the presence of various Lewis acids to afford cycloaddition products **4** or **6** respectively as a crystalline solid in moderate yields. For the sake of comparing aqueous reaction conditions to organic reaction conditions, the *in situ* generation of nitrile imines was also accomplished by treating the respective hydrazonyl chlorides **2** and **5** with an excess of triethylamine in dry dichloromethane at room temperature by following the classical nitrile imine cycloaddition protocol.^[19,20] The results of the cycloaddition reaction with respect to reaction conditions, time required for reaction completion, isolated products, and isolated yields are furnished in Tables 1 and 2.

Based upon the data in Tables 1 and 2, when **1** and **2** or **1** and **5** were vigorously stirred at room temperature in the absence of a Lewis acid promoter in an aqueous environment, no reaction was observed by TLC, and the starting materials were recovered almost quantitatively. Of the Lewis acids that were tested in Tables 1 and 2, Ag and Cu based Lewis acids consistently provided the cycloaddition products in moderate to good yields.^[10a,22] In order to investigate this methodology to a further extent, the identical Lewis acids from Tables 1 and 2 were utilized as promoters for the cycloaddition of

dipolarophiles **7**, **10**, and **13** with the nitrile imines from hydrazonyl chlorides **2** ($R = H$) and **5** ($R = OCH_3$). The data from these studies revealed that, depending upon the Lewis acid promoter that was used, dipolarophiles **7**, **10**, and **13** provided the corresponding pyrazoline products in moderate to good yields (Tables 3–5). The results of these cycloaddition reactions with respect to reaction conditions, time required for reaction completion, isolated products, and isolated yields are furnished in Tables 3, 4, and 5.

These results show that under Lewis acid activation in an aqueous environment, hydrazonyl chlorides are more prone toward nitrile imine formation and subsequent 1,3-dipolar cycloaddition than analogous reactions carried out in the absence of a Lewis acid at room temperature. Even though many of the Lewis acid promoters shown in Tables 1–5 were effective in promoting 1,3-dipolar cycloaddition reactions in acceptable time and isolated yields, an investigation of the affect surfactants have on the reaction times and isolated yields of Huisgen cyclization products in an aqueous environment was also performed to determine if the reported Lewis acid methodology is comparable to a surfactant mediated cycloaddition.

Previous reports described that 1,3-dipolar cycloaddition reactions in aqueous media between nitrile imines and dipolarophiles were best performed by shaking a heterogeneous mixture of the reactants in the presence of a base and the surfactant, tetrahexylammonium chloride (THAC), as the micellar catalyst.^[3,10a] Based on this information, we decided to introduce THAC in the aforementioned 1,3-dipolar cycloaddition reactions and determine whether THAC would promote the cycloaddition reactions in aqueous media with higher isolated cycloadduct yields and faster reaction times in comparison to the silver and copper Lewis acid catalysts. The following reaction conditions were used for the cycloaddition reactions: (i) aqueous 0.1M NaOH (method A); (ii) 80:20 mixture of aqueous 0.1M NaOH and THF (method B) and (iii) aqueous 0.1M NaOH in the presence of THAC as a catalyst (method C). All the reactions were carried out at room temperature by rigorous stirring of the reactants.^[3b] Methods A and B provided no cycloaddition products, but method C furnished the desired cycloaddition products, and the time period of these reactions typically occurred between 10–15 hrs. The yields of the reaction along with the products are furnished in Table 6. The formation of the cycloadduct from method C provides evidence that THAC is participating as a promoter in the cycloaddition reaction, and product isolation yields and the reaction times for the Lewis acid and surfactant promoted 1,3-dipolar cycloaddition reactions in water were comparable to many of the same reactions performed in dichloromethane.

Based upon experimental evidence and previous publications,^[3,5a,10a,23] the pathway that THAC and Lewis acids follow for promoting 1,3-dipolar cycloaddition reactions may be different. In aqueous solutions, surfactants, such as THAC, usually promote reactions through forming micellar aggregates. However, typically, during a 1,3-dipolar cycloaddition reaction in an organic solvent, a Lewis acid is usually used to coordinate to a conjugated electron withdrawing functional group of the dipolarophile, or undergo metal insertion at the terminal end of an alkyne which then increases the dipolarophile's reactivity toward the 1,3-dipole.^[24] In our examples, compound **7** is the only dipolarophile that has a conjugated electron withdrawing group, but because the presence of silver or copper Lewis acids were essential for all of the cycloadditions to occur in pure water at room temperature, these Lewis acids are likely participating in the 1,3-dipolar cycloaddition in a manner other than coordinating to a dipolarophile. When silver carbonate was used to generate the nitrile imine from the α -chlorohydrazone, silver can form a very strong covalent bond with a chloride ion in an aqueous solution and thereby drive the formation of a nitrile imine.^[19–21]

Even though copper does not form a strong covalent bond with chloride ions in aqueous solutions, copper can potentially assist in the dissociation of the chloride ion from α -chlorohydrazone. After interaction of the α -chlorophenyl hydrazone **2** with a copper based Lewis acid, the corresponding copper complexed intermediate **16** could form where copper can now assist in the intramolecular loss of the chloride ion to form intermediate **17** after the loss of nitric acid. The nitrile imine could then form through the formation of an additional C-N bond of **17** with concomitant loss of chloride, copper, and nitrate ions as shown in the proposed mechanism in Scheme 2.^[25] Other interactions between the ionic solution and the reactants that lead to the accelerated formation of cycloadducts are also possible.^[26] Typically, silver carbonate formed the desired cycloaddition products in less time and higher yields than copper based Lewis acids possibly due to the formation of a strong silver chloride bond and the assistance of the carbonate ion in forming the nitrile imine. However, due to the absence of insoluble silver chloride salts in the reaction mixture, isolation of the cycloadducts from copper based Lewis acids was less complicated than when silver containing Lewis acids were used. Furthermore, unlike copper Lewis acid promoted cycloadditions, the silver Lewis acids could only promote the 1,3-cycloadditions in the absence of light. The regiochemical outcome of the cycloaddition was dependent on the electronic features of both nitrile imines **2** and **5** and alkenyl dipolarophiles **1**, **7**, **10**, and **13**, and reflects the usual frontier molecular orbital controlled nature of nitrile imine cycloaddition reactions.^[27]

Conclusions

In conclusion, the results from our study show that water is a good medium for the Lewis acid promoted generation of nitrile imines and their subsequent 1,3-dipolar cycloaddition reaction with dipolarophiles. Silver and copper based Lewis acids demonstrated the highest isolated cycloadduct yields and the lowest times required for reaction completion. Furthermore, when compared to the analogous cycloaddition reactions in organic solvents, both Lewis acid and surfactant promoted aqueous cycloaddition reactions have comparable times for reaction completion, proceed at room temperature, are more environmentally benign, and the products were isolated in moderate to good yields. Future studies on the application and mechanistic details of Lewis acid cycloaddition reactions for the synthesis of other heterocyclic ring systems are in progress.

Experimental Section

General Considerations

All chemicals were purchased from commercial vendors and used without purification. Analytical TLC was performed on precoated aluminum plates (Merck silica gel 60, F254) and was visualized with UV light. Chromatography separations were carried out by flash column over Merck Silica Gel 60 (230–400 mesh), and ethyl acetate/hexane was used as eluant.

Instrumentation: IR spectra were taken on a Nicolet Model Nexus 670 FTIR spectrophotometer. Data are presented as the frequency of absorption (cm⁻¹). Only selected absorbances (ν_{max}) are reported. NMR spectra (¹H at 300 MHz, ¹³C at 75 MHz) were recorded in CDCl₃ as the solvent, and chemical shifts are reported in parts per million relative to internal solvent signal. Data are presented as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = double, t = triplet, m = multiplet, J = coupling constant in Hertz (Hz)). All HRMS samples were analyzed by positive ion electrospray on a Bruker 12 Tesla APEX -Qe FTICR-MS with an Apollo II ion source.

General Procedure for the 1,3-dipolar cycloaddition reactions in dichloromethane

To a 10 mL dry dichloromethane solution containing the disubstituted alkene (3.0 mmol) and the hydrazonyl chloride (3.0 mmol) was added triethylamine (0.463 mL, 3.3 mmol). The reaction mixture was stirred at rt until the disappearance of the starting materials, as evidenced by TLC. After the reaction was complete, the crude reaction mixture was concentrated, and the solvent was evaporated under reduced pressure. The crude products were purified by flash column chromatography over silica gel by using the required ratio of hexanes and ethyl acetate as an eluant system.

General Procedure for Lewis Acid mediated 1,3-dipolar cycloaddition reactions in water

To a capped 20 dram vial containing a solution of the disubstituted alkene (3.0 mmol) and the hydrazonyl chloride (3.0 mmol) in 10 mL of deionized water was added a Lewis acid (4.5 mmol). The reaction mixture was stirred rigorously at rt until the disappearance of the starting materials, as evidenced by TLC. The reaction mixture was extracted with ethyl acetate, washed with brine solution, dried over anhydrous Na_2SO_4 , and the solvent was evaporated under reduced pressure. The crude products were purified by flash column chromatography over silica gel by using the required ratio of hexanes and ethyl acetate as an eluant system.

When silver carbonate was used as the Lewis acid, the reaction mixture vessel was completely covered with aluminum foil to prevent light induced decomposition of the silver salts. Filtration of the reaction mixture was followed by the usual extraction process when silver carbonate was used.

General Procedure for THAC (Tetrahexyl ammonium chloride) catalyzed reactions

To a capped 20 dram vial containing a solution of the disubstituted alkene (3 mmol) and the hydrazonyl chloride (3 mmol) in 10 mL of 0.1M NaOH solution, was added tetrahexyl ammonium chloride (10.5 mmol). The reaction mixture was rigorously stirred at rt until the disappearance of the starting materials, as evidenced by TLC. The reaction mixture was passed through the celite and the filtrate was extracted with dichloromethane and concentrated, washed with brine solution, dried over anhydrous Na_2SO_4 , and the solvent was evaporated under reduced pressure. The crude products were purified by flash column chromatography over silica gel by using the required ratio of hexanes and ethyl acetate as an eluant system.

(3-Hydroxymethyl-2,5-diphenyl-3,4-dihydro-2H-pyrazol-3-yl)-methanol (11)

After column chromatography (hexanes-ethyl acetate, 1:1), this compound was obtained as a colorless liquid, IR (KBr) ν 3378, 2962, 2873, 1713, 1600 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 2.61 (br s, 2H, $-\text{CH}_2-$), 3.35 (s, 2H, $-\text{OH}$), 3.57 (d, $J = 11.5\text{Hz}$, 2H, $-\text{CH}_2\text{OH}$), 3.71 (d, $J = 11.5\text{Hz}$, 2H, $-\text{CH}_2\text{OH}$), 6.96 (t, $J = 6\text{Hz}$, 1H, $N\text{-ArH}$), 7.19 (s, 4H, $N\text{-ArH}$), 7.32–7.35 (m, 3H, ArH), 7.65–7.67 (m, 2H, ArH); ^{13}C NMR (75 MHz, CDCl_3): δ 40.7, 64.6(2C), 74.5, 119.1(2C), 123.2, 126.2(2C), 128.8(2C), 129.1, 129.2(2C), 132.7, 144.7, 150.3. HRMS (EI): m/z calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2\text{Na}^+$ (MNa^+): 305.1260; found: 305.1258.

[3-Hydroxymethyl-5-(4-methoxy-phenyl)-2-phenyl-3,4-dihydro-2H-pyrazol-3-yl]-methanol (12)

After column chromatography (hexanes-ethyl acetate, 1:1), this compound was obtained as a colorless liquid, IR (KBr) ν 3390, 2929, 1709, 1609, 1517 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 2.52 (br s, 2H, $-\text{CH}_2-$), 3.33 (s, 2H, $-\text{OH}$), 3.56 (d, $J = 11.4\text{Hz}$, 2H, $-\text{CH}_2\text{OH}$), 3.71 (d, $J = 11.4\text{Hz}$, 2H, $-\text{CH}_2\text{OH}$), 3.80 (s, 3H, $-\text{OCH}_3$), 6.87 (d, $J = 8.7\text{Hz}$, 2H, ArH), 6.96 (t, $J = 6.5\text{Hz}$, 1H, $N\text{-ArH}$), 7.16–7.24 (m, 4H, $N\text{-ArH}$), 7.60 (d, $J = 8.6\text{Hz}$, 2H, ArH); ^{13}C

NMR (75 MHz, CDCl₃): δ 41.8, 47.5(2C), 55.6, 72.8, 114.3(2C), 120.3(2C), 123.6, 125.2, 127.6(2C), 129.3(2C), 143.7, 147.8, 160.6; HRMS (EI): m/z calcd. for C₁₈H₂₀N₂O₃Na⁺ (MNa⁺): 335.1366; found: 335.1360.

5,5-Bis-chloromethyl-1,3-diphenyl-4,5-dihydro-1H-pyrazole (14)

After column chromatography (hexanes-ethyl acetate, 8:2), this compound was obtained as colorless liquid, IR (KBr) ν 3396, 3057, 2934, 1726, 1593, 1565 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 3.60 (s, 2H, -CH₂-), 3.81–3.92 (m, 4H, -CH₂Cl), 7.1 (t, J = 7.5Hz, 1H, *N*-ArH), 7.28–7.46 (m, 7H, ArH, *N*-Ar H), 7.77 (d, J = 9.2Hz, 2H, ArH); ¹³C NMR (75 MHz, CDCl₃): δ 41.6, 47.5(2C), 73.1, 120.4(2C), 123.8, 126.0(2C), 128.8(2C), 129.2, 129.4(2C), 132.4, 143.4, 147.8, HRMS (EI): m/z calcd for C₁₇H₁₆Cl₂N₂H⁺ (MH⁺): 319.0763; found: 319.0763.

5,5-Bis-chloromethyl-3-(4-methoxy-phenyl)-1-phenyl-4,5-dihydro-1H-pyrazole (15)

After column chromatography (hexanes-ethyl acetate, 7:3), this compound was obtained as dark brown oil, IR (KBr) ν 3516, 3011, 2883, 2405, 1612, 1511 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 3.52 (s, 2H, -CH₂-), 3.75–3.86 (m, 7H, -OCH₃, -CH₂Cl), 6.90 (d, J = 8.8Hz, 2H, *C*-Ar H), 7.05 (t, J = 11Hz, 1H, *N*-ArH), 7.21–7.33 (m, 4H, *N*-ArH), 7.66 (d, J = 8.8Hz, 2H, ArH); ¹³C NMR (75 MHz, CDCl₃): δ 41.8, 47.4(2C), 55.5, 72.8, 114.2(2C), 120.2(2C), 123.5, 125.1, 127.5(2C), 129.3(2C), 143.6, 147.8, 160.6; HRMS (EI): m/z calcd for C₁₈H₁₈Cl₂N₂OH⁺ (MH⁺): 349.0868; found: 349.0871.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.

Pyrazole and spiro-pyrazoline syntheses through a Lewis acid catalyzed 1,3-dipolar cycloaddition in water.

Scheme 2.

Proposed mechanistic rationale for the formation of a nitrile imine from **2** and copper nitrate in water.

Table 1Product and yields for the Huisgen cyclization of **1** and hydrazonyl chloride (**2**)

Entry	Lewis Acid (or) Reagent/Solvent	Time (hrs)	Product	Yield (%)
1	None/H ₂ O	—	4	N.R. ^I
2	(C ₂ H ₅) ₃ N/CH ₂ Cl ₂	6	4	88
3	LiNO ₃ /H ₂ O	9	4	71
4	Cu(NO ₃) ₂ /H ₂ O	8	4	68
5	Ag ₂ CO ₃ /H ₂ O	7	4	77
6	CuSO ₄ x 5H ₂ O/H ₂ O	6	4	23

^I N.R. = No Reaction was observed

Table 2Product and yields for the Huisgen cyclization of **1** and hydrazonoyl chloride (**5**)

Entry	Lewis Acid (or) Reagent/Solvent	Time (hrs)	Product	Yield (%)
7	None/H ₂ O	–	6	N.R. ^I
8	(C ₂ H ₅) ₃ N/CH ₂ Cl ₂	11	6	68
9	LiNO ₃ /H ₂ O	14	6	71
10	Cu(NO ₃) ₂ /H ₂ O	15	6	72
11	Ag ₂ CO ₃ /H ₂ O	13	6	74
12	CuSO ₄ x 5H ₂ O/H ₂ O	12	6	83

^I N.R. = No Reaction was observed

Table 3

Product and yields for the Huisgen cyclization of **7** with hydrazonyl chlorides (**2** and **5**)

Entry	Lewis Acid or Reagent/Solvent	α -Chlorohydrazone	Time (hrs)	Product	Yield (%)
13	None/H ₂ O	R = H	–	8	N.R. ^I
14	(C ₂ H ₅) ₃ N/CH ₂ Cl ₂	R = H	9	8	77
15	LiNO ₃ /H ₂ O	R = H	10	8	16
16	Cu(NO ₃) ₂ /H ₂ O	R = H	12	8	31
17	Ag ₂ CO ₃ /H ₂ O	R = H	11	8	52
18	CuSO ₄ x 5H ₂ O/H ₂ O	R = H	10	8	8
19	None/H ₂ O	R = OCH ₃	–	8	N.R. ^I
20	(C ₂ H ₅) ₃ N/CH ₂ Cl ₂	R = OCH ₃	7	9	88
21	LiNO ₃ /H ₂ O	R = OCH ₃	9	9	28
22	Cu(NO ₃) ₂ /H ₂ O	R = OCH ₃	9	9	57
23	Ag ₂ CO ₃ /H ₂ O	R = OCH ₃	8	9	51
24	CuSO ₄ x 5H ₂ O/H ₂ O	R = OCH ₃	9	9	63

^I N.R. = No Reaction was observed

Table 4Product and yields for the Huisgen cyclization of **10** with hydrazone chlorides (**2** and **5**)

Entry	Lewis Acid or Reagent/solvent	α -Chlorohydrazone	Time (hrs)	Product	Yield (%)
25	None/H ₂ O	R = H	--	11	N.R. [/]
26	(C ₂ H ₅) ₃ N/CH ₂ Cl ₂	R = H	10	11	95
27	LiNO ₃ /H ₂ O	R = H	--	11	N.R. [/]
28	Cu(NO ₃) ₂ /H ₂ O	R = H	12	11	45
29	Ag ₂ CO ₃ /H ₂ O	R = H	11	11	69
30	CuSO ₄ x 5H ₂ O/H ₂ O	R = H	10	11	48
31	None/H ₂ O	R = OCH ₃	--	12	N.R. [/]
32	(C ₂ H ₅) ₃ N/CH ₂ Cl ₂	R = OCH ₃	11	12	89
33	LiNO ₃ /H ₂ O	R = OCH ₃	--	12	N.R. [/]
34	Cu(NO ₃) ₂ /H ₂ O	R = OCH ₃	13	12	58
35	Ag ₂ CO ₃ /H ₂ O	R = OCH ₃	--	12	N.R. [/]
36	CuSO ₄ x 5H ₂ O/H ₂ O	R = OCH ₃	12	12	54

[/] N.R = No Reaction was observed

Table 5

Product and yields for the Huisgen cyclization of **13** with hydrazonyl chlorides (**2** and **5**)

Entry	Lewis Acid or Reagent/solvent	α -Chlorohydrazone	Time (hrs)	Product	Yield (%)
37	None/H ₂ O	R = H	--	14	N.R. ^I
38	(C ₂ H ₅) ₃ N/CH ₂ Cl ₂	R = H	8	14	91
39	LiNO ₃ /H ₂ O	R = H	--	14	N.R. ^I
40	Cu(NO ₃) ₂ /H ₂ O	R = H	13	14	65
41	Ag ₂ CO ₃ /H ₂ O	R = H	8	14	73
42	CuSO ₄ x 5H ₂ O/H ₂ O	R = H	11	14	61
43	None/H ₂ O	R = OCH ₃	--	15	N.R. ^I
44	(C ₂ H ₅) ₃ N/CH ₂ Cl ₂	R = OCH ₃	11	15	96
45	LiNO ₃ /H ₂ O	R = OCH ₃	--	15	N.R. ^I
46	Cu(NO ₃) ₂ /H ₂ O	R = OCH ₃	11	15	56
47	Ag ₂ CO ₃ /H ₂ O	R = OCH ₃	10	15	89
48	CuSO ₄ x 5H ₂ O/H ₂ O	R = OCH ₃	12	15	67

^I N.R. = No Reaction was observed

Table 6

Tetrahexylammonium chloride (THAC) mediated Huisgen cyclization reactions

Entry	Dipolarophile	α -Chlorohydrazone	Time (hrs)	Product	Yield (%)
49	1	2	15	4	85
50	1	5	14	6	66
51	7	2	12	8	68
68	7	5	11	9	70
52	10	2	10	11	62
53	10	5	13	12	23
54	13	2	10	14	75
55	13	5	10	15	40