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Note

A green approach in aqueous phase synthesis of isoxazolidine derivatives from N-phenyl-α-amino nitrone and their antibacterial activities

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1,3 Dipolar cycloaddition reaction of N-phenyl-α-amino nitrone with different dipolarophiles have been studied in water for the synthesis of novel isoxazolidines. Significant change in rate acceleration and high yield of these reactions are observed in water compared to organic solvents. All the synthesized compounds have been screened for their antibacterial activity and found to exihibit significant activity.

Keywords: N-phenyl-α-amino nitrone, aqueous phase synthesis, high yield, antibacterial activity.

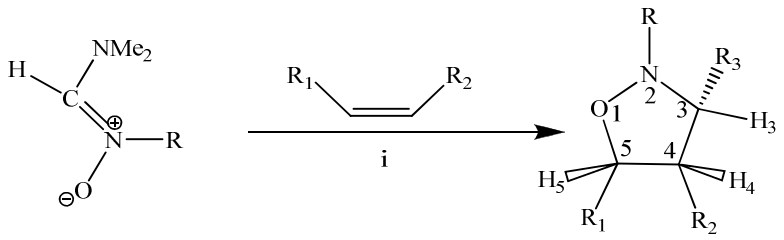
Organic solvent free reactions have attracted considerable interest due to increasing awareness about environmental problems in chemical research and industry[1]. Water as the reaction medium is generally considered as a cheap, safe and environmentally benign alternative to organic solvents[2,3]. This prompted the systematic investigation into the feasibility of organic solventless reactions in aqueous media under mild conditions. 1,3 Dipolar cycloaddition reaction between a nitrone and an olefinic dipolarophile is an efficient method for the synthesis of the isoxazolidine ring system[4]. Furthermore, the cycloadducts have found numerous applications in synthesis through reductive cleavage of the N-O bond to give γ amino alcohols[4] while nitrones can be used as an oxidizing agent for the synthesis of aldehydes[5]. Asymmetric induction in nitrone-olefin cycloadditions has been achieved through incorporation of chirality in both the dipole and dipolarophile[6]. Due to unstability of nitrones very few examples of the isolation or detection of the nitrones have been reported and are usually trapped in-situ by different dipolarophiles in 1,3 dipolar cycloaddition reaction to afford cycloadducts[4]. Preliminary reports about the synthesis and cycloaddition reactions of N-phenyl-α-amino nitrone **1** in organic solvent has been already reported[7].

In continuation of our studies in aqueous phase isoxazolidine synthesis using α-chloro nitrones[8], the present paper reports on the synthesis and antibacterial activities of some novel isoxazolidine derivatives derived from nitrone **1** in water with high yield in a very short reaction time (**Scheme I**, **Table I**). For the present study, we have used three different maleimides, ethyl acrylate and methyl vinyl ketone (electron poor and electron rich dipolarophiles) so as to study the nature of the cycloaddition reactions and the stereochemistry of isoxazolidine derivatives. Almost all the reactions in water are very fast (4-5 hr in case of maleimides and 5 hr for other olefins) compared to the cycloaddition reactions carried out in organic solvents (THF) which were reported to take longer periods (26-48 hr) (ref. 7). It was observed that the reactions in common organic solvents such as THF or CH_2Cl_2 under identical reaction conditions were very slow and proceeded only partially even after 10–15 hr (ref. 7) (**Table I**). Hence this is a very simple and greener procedure for cycloaddition reaction in the isoxazolidine synthesis. The amount of water used in the reaction did not have any significant influence on the overall rate of the reaction and yield of the products[9]. It is possible that water promotes the reaction through hydrogen bond formation with the carbonyl oxygen atom of the α,β unsaturated carbonyl compounds and thereby increasing the eletrophilic character at the β carbon which is attacked by nucleophilic oxygen atom of the nitrone. Thus water activates the maleimides, ethyl acrylate, methyl vinyl ketone and thereby greatly facilitates the reaction.

Results and Discussion

Excellent example of introduction of chirality has been observed in nitrone additions described here. The addition of nitrone **1** to maleimides and ethyl acrylate, methyl vinyl ketone result isoxazolidine derivatives (**2–6**) where as many as two to three asymmetric centers are introduced in a single step. Like most of the nitrones reported from our laboratory[10-15], nitrone **1** is also found to have

Z configuration. Cycloaddition of Z nitrone via an exo transition state geometry (**Figure 1**) results in the formation of syn isoxazolidine derivatives[16]. The relative configurations of C-3, C-4 and C-5 protons in the adducts are in favour of the exo transition state geometry. The protons at C-3, C-4, C-5 are syn in the cycloadducts **2–4** and their coupling constants ($J_{3,4}$ = 6–8 Hz; $J_{4,5}$ = 6–8 Hz) are also indicative of this stereochemical relationship[17,18]. The stereochemical assignments of **5** and **6** at C-3, C-4, C-5 of the isoxazolidines are also determined from ^{1}H NMR spectra. The coupling constant values ($J_{3,4}$ = 6–9 Hz; $J_{4,5}$ = 6–8 Hz) also revealed the formation of syn isoxazolidines in both the cases via exo transition state[16,17]. Due to the 4,5 fused pyrrolidindione, the isoxazolidine ring adopts an envelope conformation and allowing for inversion, its nitrogen atom will either extend out from the envelope, ie, minor conformation, or point inside the envelope, ie, major conformation (**Figure 2**). The minor conformer has the N-lone pair antiperiplanar and therefore capable of shielding 3-H proton, so this conformation is assigned to as minor conformer (**Figure 2**). The concerted nature of these cycloaddition reactions with nitrone as 1,3 dipole is generally accepted. The regioselectivity in these reactions are rationalized using frontier-orbital theory[19]. The ethyl acrylate, methyl vinyl ketone follows this theory. Therefore, the 5-substituted adducts for ethyl acrylate and methyl vinyl ketone is due to LUMO (nitrone)–HOMO (dipolarophile) interaction. Cycloadditions to α,β unsaturated carboxylic acid derivatives, eg ethyl acrylate are particularly useful because high regioselectivity is often observed in water[3]. The reactions were found to be highly regioselective to form solely 5 substituted isoxazolidines respectively. Considering the ^{1}H NMR spectrum of cycloadducts **5** and **6**, it has been found that clear double doublet signal for H-4 protons and triplet signal for H-3 protons were obtained for the cycloadducts and hence



1 **2 - 6**

Scheme I - Reagents and conditions : i) water, RT, 4 - 5 hr, N_2 atmosphere

2 : R_1, R_2 = -CONMeCO-
3 : R_1, R_2 = -CONEtCO-
4 : R_1, R_2 = -CON-4-OMePhCO-
5 : R_1 = $-CO_2C_2H_5$; R_2 = H
6 : R_1 = $-COCH_3$; R_2 = H

R = Ph ; R_3 = - NMe_2

Table I — Physicochemical data of the synthesized compounds

Entry	Nitrone	Dipolarophile[a]	Time (hr)	Cycloadduct[b] & m.p (^{0}c)	Yield[c] (%)
1	N-phenyl-α-amino nitrone	N-methyl maleimide	4 (44)	2 : White solid, 109	96 (57)
2	N-phenyl-α-amino nitrone	N-ethyl maleimide	4 (38)	3 : Yellow solid, 124	94 (54)
3	N-phenyl-α-amino nitrone	4-MeO-N-phenyl maleimide	5 (41)	4 : Dark yellow crystals, 88	95 (62)
4	N-phenyl-α-amino nitrone	Ethyl acrylate	5 (40)	5 : White gummy liquid	93 (60)
5	N-phenyl-α-amino nitrone	Methyl vinyl ketone	5 (42)	6 : Pale yellow oil	91 (55)

[a] Reaction condition: α-Amino nitrone (1 mmole), dipolarophile (1 equivalent), water, N_2 atmosphere, RT.
[b] All the compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, MS, HRMS spectral data.
[c] Isolated yield after purification. Yields and time in parentheses represent reactions carried out in THF.

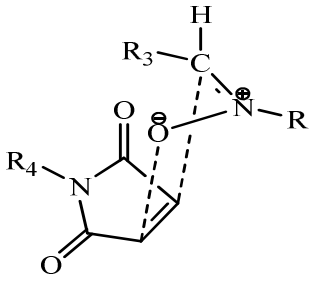
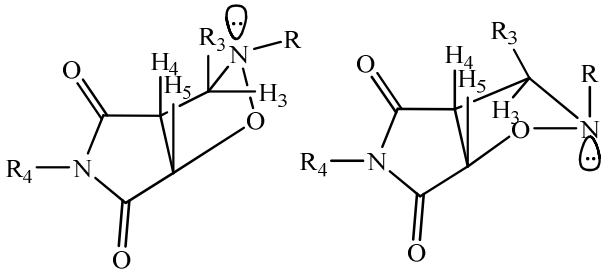


Figure 1



Minor conformation 1 Major conformation 2

R = Ph; R_3 =-NMe_2; R_4 = Me; Et; 4-OMe-C_6H_4

Figure 2

confirms in favour of 5 substituted adducts. Detail investigation on the nature of these cycloaddition reactions from TLC and ^{1}H NMR spectrum studies for the cycloadducts **5** and **6,** it was also confirmed that no 4-substituted adducts were formed. The relative configurations of H-3, H-4 and H-5 protons in these adducts are syn and the cycloadducts are in favour of exo transition state geometry as evidenced from their coupling constant values ($J_{4,5}$ = 6–9 Hz; $J_{3,4}$ = 6–8 Hz)[17,18]. Similar cycloaddition reactions of nitrone with these dipolarophiles usually give both 5 and 4 substituted adducts in conventional solvents with some exceptions of either 5 or 4 substituted adducts[4].

In general, the reactions are very clean and high yielding compared to usual cycloaddition reactions of nitrones. The products were characterized from their spectroscopic (IR, ^{1}H NMR, HRMS, ^{13}C NMR) data. No catalyst or co-organic solvent was required. In the ^{13}C NMR spectrum, four signals were obtained in case of phenyl ring carbons due to equivalent nature of C-2 and C-6 and C-3 and C-5 carbons. In the mass spectrum, significant base peak value at 107 due to the development of PhNO was obtained in the maleimide cycloadducts while base peak value at 190 due to elimination of $CH_3CH_2COO^{\cdot}$ and $CH_3CO^{\cdot}$ followed by $H^{\cdot}$ in ethyl acrylate and methyl vinyl ketone was obtained. Studies of HRMS spectra shows almost exact mass in the isolated compounds.

Antibacterial screening test

All the synthesized cycloadducts **2–6** were subjected to *invitro* screening against *Vibrio parahaemolyticus, Klebsiella pneumoniae, Bacillus subtilis, Proteus vulgaris, Staphylococcus aureus, Shigella flexneri, Eschericia coli, Salmonella typhi* and *Vibrio cholerase*. The minimum inhibitory concentration (MIC) was determined using cup plate assay method according to the standard procedure[20]. Nutrient agar was used as a culture medium. At first strains of desired bacteria were isolated and were suspended in normal saline. From each bacterial suspension 0.1 mL was taken with the help of pipette and was spread on preprepared nutrient agar plate, with the help of spreader. Then cups were scooped out from each plate with the help of a cork borer and then to the respective cups different derivatives of the isoxazolidine (**2-6**) of concentrations (1000 µg/mL, 600, 400, 200, 100, 50, 25, 10 µg/mL) were added. The plates were incubated at 37ºC for 24 hr and then results were recorded. The lowest concentration, which showed no visible growth, was taken as an end point minimum inhibitory concentration (MIC). All the compounds showed MIC 10 µg/mL except **6** which showed MIC 50 µg/mL against *Bacillus subtilis* and *Proteus vulgaris*. It has been observed that the derivatives of isoxazolidine (**2-6**) have antibacterial activity against both gram positive (*S. aureus, B. subtilis*) and gram negative (*E. coli, S. flexneri*) bacteria, hence it can be concluded that the derivatives used were broad spectrum antibiotics[20]. The MIC value obtained for isoxazolidine derivatives ranges from 10-50 µg/mL are very close to the MIC values of most commonly used antibiotics like Penicillin (10 units), Sulphonamide (300 µg/mL), Nalidixic Acid (512 µg/mL) etc and hence they are equally effective and can be prescribed after testing of LD_{50} (ref. 21).

Experimental Section

Melting points were determined in open capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded with a Bruker Avance DPX 400 spectrometer (400 MHz, FT NMR) using TMS as internal standard. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz. The coupling constants (*J*) are given in Hz. IR spectrum were obtained with a Perkin-Elmer RX 1-881 machine as film or as KBr pellets for all the products. MS spectra were recorded with a Jeol SX-102 (FAB) instrument.

The HRMS spectra were recorded on a Q – Tof micro instrument (YA – 105). TLC was carried out on Fluka silica gel TLC cards. N-methyl, N-ethyl, 4-methoxy-N-phenyl maleimides were purchased from Aldrich Chemical company and were used as received. All other reagents and solvents were purified after receiving from commercial suppliers. N-phenylhydroxylamine was prepared following standard methods available in the literature and has been used already for the synthesis of α-chloro nitrones and cycloaddition reactions involving α-amino nitrones in organic solvents[10-15].

General procedure for cycloaddition reaction in water

In a 50 mL conical flask, nitrone **1** (1 mmole), dipolarophile (1 mmole) and water (15 mL) was taken and stirred at RT with a magnetic stirrer under N_2 atmosphere for 4-5 hr. The progress of the reaction was monitored by TLC. After completion of the reaction, the products were extracted with ether (2 × 25 mL), the organic layer was washed with brine water (2 × 15 mL), dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The crude product was purified by silica gel column chromatography using ethyl acetate-hexane to afford cycloadducts (**Scheme I**). This procedure was followed for the substrates **1**–**5** listed in **Table I**.

Synthesis of (3R)-3-(dimethylamino)-5-methyl-2-phenyldihydro-2*H*-pyrrolo[3,4-d]isoxazole-4,6 (5H, 6aH)-dione 2

To a stirred solution of nitrone **1** (1 mmole) in 15 mL water was added N-methyl maleimide (1 equivalent) at RT under nitrogen atmosphere and the reaction-mixture was stirred for 4 hr. The progress of the reaction was monitored by TLC (R_f = 0.40). The crude product was extracted with ether (2 × 25 mL), the organic layer was washed with brine water (2 × 15 mL), dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The crude product was purified by silica gel column chromatography using ethyl acetate-hexane and finally obtained under reduced pressure as white solid. Yield 96%; IR ($CHCl_3$): 3150-3094 (br), 2860 (m), 1764 (s), 1655 (s), 1452 (s), 1265 (m), 785 (s) $cm^{-1;}$ ^1H NMR ($CDCl_3$): δ 7.30–7.18 (m, 5H, C_6H_5), 5.14 (d, 1H, *J* = 6.24 Hz, C_5H), 3.80 (d, 1H, *J* = 8.14 Hz, C_3H), 3.47 (dd, 1H, *J* = 6.70, 7.46 Hz, C_4H), 2.80–2.66 (br, 6H, NMe_2), 1.30 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 204.00, 200.40 (carbonyl carbons), 132.45, 131.00, 130.00, 128.80 (phenyl carbons), 87.00 (C_5), 76.70 (C_3), 58.00 (C_4), 43.40, 41.50 (NMe_2), 15.00 (CH_3); FAB-MS (m/z): 275 (M^+), 260, 198, 183, 168, 154, 148, 147, 107 (B.P), 77; HRMS–EI: Calcd. for $C_{14}H_{17}O_3N_3$ (M), 275.3080, Found: M^+, 275.3064.

Synthesis of (3R)-3-(dimethylamino)-5-ethyl-2-phenyldihydro-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6 (5H, 6aH)-dione 3

To a stirred solution of nitrone **1** (1 mmole) in 15 mL water was added N-ethyl maleimide (1 equivalent) at RT under nitrogen atmosphere and the reaction-mixture was stirred for 4 hr. The progress of the reaction was monitored by TLC (R_f = 0.42). The product was extracted with ether (2 ×25 mL), the organic layer was washed with brine water (2 ×15 mL), dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The crude product was purified by silica gel column chromatography using ethyl acetate-hexane and finally obtained under reduced pressure as yellow solid.Yield 94 %; IR ($CHCl_3$):3165-3082 (br), 3013 (m), 2865 (m), 1760 (s), 1660 (m), 1445 (s), 1280 (m), 778 (s) $cm^{-1;}$ ^1H NMR ($CDCl_3$): δ 7.45 – 7.31 (m, 5H, C_6H_5), 5.26 (d, 1H, *J* = 8.20 Hz, C_5H), 3.62 (d, 1H, *J* = 7.20 Hz, C_3H), 3.38 (dd, 1H, *J* = 6.16, 6.32 Hz, C_4 2H), 2.90 – 2.78 (br, 6H, NMe_2), 2.66 (q, 2H, *J* = 6.12, 6.80 Hz, CH_2CH_3), 1.34 (t, 3H, *J* = 7.10 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$): δ 200.40, 197.80 (carbonyl carbons), 136.50, 135.00, 133.20, 131.80 (phenyl carbons), 86.20 (C_5), 78.40 (C_3), 55.00 (C_4), 41.70, 39.64 (NMe_2), 23.50 (CH_2CH_3), 14.00 (CH_2CH_3); FAB-MS: m/z 289 (M^+), 260, 212, 182, 168, 148, 141, 107 (B.P), 77; HRMS–EI: Calcd. for $C_{15}H_{19}O_3N_3$ (M), 289.3350, Found; M^+, 289.3334.

Synthesis of (3R)-3-(dimethylamino)-5-(4-methoxyphenyl)-2-phenyldihydro-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6 (5H, 6aH)-dione 4

To a stirred solution of nitrone **1** (1 mmole) in 15 mL water was added 4-methoxy-N-phenyl maleimide (1 equivalent) at RT under nitrogen atmosphere and the reaction-mixture was stirred for 5 hr. The progress of the reaction was monitored by TLC (R_f = 0.39). The product was extracted with ether (2 × 25 mL), the organic layer was washed with brine water (2 × 15 mL), dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The crude product was purified by silica gel column chromatography using

ethyl acetate-hexane and finally obtained under reduced pressure as dark yellow crystals. Yield 95 %; IR ($CHCl_3$) : 3084-3022 (br), 2880 (m), 1765 (s), 1650 (s), 1472 (m), 1365 (m), 795 (s), 775 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.55-7.40 (m, 5H, C_6H_5 protons), 6.90 – 6.78 (m, 4H, phenyl protons), 5.40 (d, 1H, *J* = 8.24 Hz, C_5H), 3.82 (d, 1H, *J* = 7.28 Hz, C_3H), 3.54 (dd, 1H, *J* = 9.24, 6.08 Hz, C_4 2H), 3.30 (s, 3H, OCH_3), 2.70–2.56 (br, 6H, NMe_2); ^{13}C NMR ($CDCl_3$): δ 204.50, 198.65 (carbonyl carbons), 138.00, 137.00, 135.64, 134.32, 133.70, 132.00, 131.46, 130.00 (aromatic carbons), 85.50 (C_5), 76.00 (C_3), 59.42 (C_4), 54.60 (OCH_3), 40.75, 38.20 (NMe_2); FAB-MS: m/z 351 (M^+), 320, 274, 244, 230, 167, 148, 107 (B.P), 77; HRMS – EI: Calcd. for $C_{20}H_{21}O_4N_3$, (M), 351.4060, Found; M^+, 351.4044.

Synthesis of (3R)-ethyl 3-(dimethylamino)-2-phenyl isoxazolidine-5-carboxylate 5

To a stirred solution of nitrone **1** (1 mmole) in 15 mL water was added ethyl acrylate (1 equivalent) at RT under nitrogen atmosphere and the reaction-mixture was stirred for 5 hr. The progress of the reaction was monitored by TLC (R_f = 0.48). The product was extracted with ether (2 × 25 mL), the organic layer was washed with brine water (2×15 mL), dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The crude product was purified by silica gel column chromatography using ethyl acetate-hexane and finally obtained under reduced pressure as white gummy liquid. Yield 93%; IR ($CHCl_3$): 3155–3060 (br), 2930 (s), 2856 (m), 1750 (s), 1445 (s), 1340 (m), 770(s) cm^{-1}; ^{1}HNMR ($CDCl_3$): δ 7.20-7.08 (m, 5H, C_6H_5), 4.80 (t, 1H, *J* = 8.2 Hz, C_5H), 4.26 (q, 2H, *J* = 6, 6.02 Hz, -O*CH*$_2$CH$_3$), 3.58 (t, 1H, *J* = 7.22 Hz, C_3H), 3.24 (dd, 2H, *J* = 8.40, 7.08 Hz, C_4 2H), 2.76 – 2.65 (br, 6H, NMe_2), 1.24 (t, 3H, *J* = 7.50 Hz, -OCH$_2$*CH*$_3$); ^{13}C NMR ($CDCl_3$): δ 170.40 (carbonyl carbon), 135.00, 134.00, 132.25, 130.60 (aromatic carbons), 87.50 (C_5), 76.30 (C_3), 70.40 (CH_2 carbon of -OCH_2CH_3), 57.00 (C_4), 44.50, 42.80 (NMe_2), 20.00 (CH_3 carbon of OCH_2CH_3); FAB-MS: m/z 264 (M^+), 190 (B.P), 187, 157, 148, 143, 116, 107, 77; HRMS-EI: Calcd. for $C_{14}H_{20}O_3N_2$ (M): 264.3250; Found (M^+), 264.3239.

Synthesis of 1-((3R)-3-(dimethylamino)-2-phenyl-isoxazolidin-5-yl)ethanone 6

To a stirred solution of nitrone **1** (1 mmole) in 15 mL water was added methyl vinyl ketone (1 equivalent) at RT under nitrogen atmosphere and the reaction-mixture was stirred for 5 hr. The progress of the reaction was monitored by TLC (R_f = 0.44). The product was extracted with ether (2 × 25 mL), the organic layer was washed with brine water (2 × 15 mL), dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The crude product was purified by silica gel column chromatography using ethyl acetate-hexane and finally obtained under reduced pressure as pale yellow oil.Yield 91%; IR ($CHCl_3$): 3172 – 3033 (br), 2936 (s), 1720 (s), 1442 (m), 1235 (s), 780 (s) $cm^{-1;}$ ^1H NMR ($CDCl_3$): δ 6.80 – 6.68 (m, 5H, C_6H_5), 4.86 (t, 1H, *J* = 7.14 Hz, C_5H), 3.74 (t, 1H, *J* = 6.80 Hz, C_3H), 3.38 (dd, 2H, *J* = 8.80, 7.40 Hz, C_4 2H), 2.82 – 2.70 (br, 6H, NMe_2), 2.16 (s, 3H, $COCH_3$); ^{13}C NMR ($CDCl_3$): δ 202.50 (carbonyl carbon), 133.55, 132.00, 130.86, 129.20 (aromatic carbons), 88.70 (C_5), 76.00 (C_3), 58.45 (C_4), 42.40, 40.00 (NMe_2), 31.20 (methyl carbon of $COCH_3$); FAB-MS: m/z 234 (M^+), 190 (B.P), 157, 147, 113, 107, 77; HRMS-EI: Calcd. for $C_{13}H_{18}O_2N_2$ (M): 234.2990; Found (M^+), 234.2978.

Conclusion

In summary, the present procedure provides an example of green chemistry methodology for the synthesis of regio and stereoselective novel isoxazolidines in aqueous phase with high yield in a short reaction time and all the synthesized compounds are having significant antibacterial activities. The notable factors of this methodology are: (a) high yields (b) much faster reaction (c) mild reaction conditions and (d) green synthesis avoiding use of organic solvents. Therefore, it is believed that the procedure described here will find important applications in the synthesis of isoxazolidine derivatives and thereby offering greater scope for aqueous phase cycloaddition reactions.

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