Novel synthesis of 1,5-disubstituted-1,2,3-triazolines catalysed by Zepto™ magnetic microspheres under the influence of rotating magnetic field

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Abstract:

The novel reactor has been designed to perform chemical reactions under the influence of magnetic field generated by alternating magnetic poles as a function of time and successfully employed the system to synthesize a series of 1,5-disubstituted-1,2,3-triazolines *via* the regioselective [3+2] cycloaddition reactions between alkyl/aryl azides and nitroolefins catalysed by Zepto^{TM} (para magnetic ultra-blue carboxy functionalized) microspheres (bead diameter 2.5 μm). All the reactions went smoothly without any adverse effect on nitro, cyano, thienyl, hydroxy, halogens and ether functions at 25±2°C, to afford 82-99% pure products at magnetic field and exposure time of 18.99 mT and 180-240 min. The influence of magnetic force exerted on the magnetic materials was found to enhance the catalytic activity of microspheres. The catalyst could easily be separated by simple centrifugation which could be reused for atleast 15 runs with no loss in activity.

Keywords: 1,2,3- Triazolines, magnetic field, Novel reactor, magnetic microspheres

Introduction

1,2,3-Triazole scaffold has become a treasury of bioactive compounds and therefore, chemists and biochemists have been engaged in the derivatisation of the moiety and screening them for further exploration[1].1,2,3-triazoles are the best amide surrogates in bioactive compounds due to their strong dipole moments[2]. They also serve as a linker and exhibit bio-isosteric effects on peptide linkage, imidazole ring, aromatic ring and double bonds[3]. These motifs are effective in the formation of hydrogen bonds and dipole-dipole interactions facilitating the binding capacity of the drug molecules with the target virus[4]. Due to these facts, 1,2,3-Triazolesarewell-known to possess a broad spectrum of bio-activities like antifungal[5], antiviral against orthopoxviruses and severe acute respiratory syndrome[6], antibacterial[7] and anticancer activities [8]. Peng and co-workers have recently synthesized 3-arylethylnyltriazolyl ribonucleosides and reported the tolyl derivative to have potent anticancer activity on the drug-resistant pancreatic cancer cell line MiaPaca-2[9]. Very recently Phokodylo *et al* have conjugated oxadiazoles and thiazole with 1,2,3-triazole and demonstrated these compounds to be active against melanoma, colon and breast cancer[10]. Furthermore, 1,2,3-Triazoles have drawn interest of synthetic chemists for their precursors in the construction of novel bio-molecules[11]. In the year 1961, Rolf Huisgen was successful in an attempt for the synthesis by 1,3- dipolar cycloaddition reaction of organic azides with alkynes which afforded both the isomers such as 1,4-disubstituted and 1,5- disubstituted 1,2,3-triazoles and couldn't be separated[12]. Later developments to modify Huisgen's reaction to achieve regio-selective syntheses, number of methodologies have been established for 1,4- disubstituted-1,2,3-triazoles[13-15] and 1,5-disubstituted 1,2,3-triazoles[16-22]. Compared to 1,4- disubstituted-1,2,3-triazoles, 1,5- disubstituted-1,2,3-triazoles have shown multiple biological activities. For example, uracil and tert-amide derivatives of 1,5-isomer showed Human dUTPase Inhibitory activity[23], the nucleoside derivative shown non-nucleoside reverse transcriptase inhibitor tertbutyldimethylsilylspiroaminooxathioledioxide (TSAO)[24], antimicrobial and anti-cancer activity by carboxyamidotriazole (CAI)[9]. The potential drugs based on 1,5-disubstituted 1,2,3-triazoles are presented in figure 1.

Therefore, it is worth to synthesize 1,5-isomer but obtaining 1,5-isomer is still a challenge. There have been continued efforts in achieving regio-specific 1,5- disubstituted-1,2,3-triazoles[25]. Typical routes include the use of in situ generated sodium, lithium, tin, germanium or magnesium acetylides[17,26]. These reactions involve the use of large excess of strong bases and thus produce undesirable chemical waste. There are also the reports which use highly expensive ruthenium and other noble metal complexes[26c] which are either difficult to obtain in ordinary laboratories or which is economically unviable and the use of Raney Nickel which is air sensitive and the reaction need to be run under extensive care and precautions and the procedure can never be used to for the production in multi-gram scale[26b]. Other procedures require harsh conditions and elevated temperatures using oil bath[26f] and too much time consuming and cumbersome work-up procedures[25a, 27,28]. On the other hand, owing to its wide spectrum of diverse applications, magnetic field (MF) is playing major roles in current science and technology[29]. MF has been utilized in the areas of therapeutic and diagnostic medicine, environmental management and industries over the years[30]. Addressing environmental issues including water treatment using magnetic technique has also received substantial consideration in recent times[31,32]. Very recently, Junk*a et. al* have reported in nature science, the application of rotating magnetic fields to increase the activity of antimicrobials against wound biofilm pathogens[33].

Experimental

Materials

Zepto^{TM} carboxy functionalized polystyrene magnetic fluorescent ultra-blue microspheres with emission at 450 nm (lot number 2457883_M1) was obtained from cytodiagnostics, Nitroolefins were synthesized according to a previous procedure[35]. All the solvents were of analytical grade and used without further purification. Thin layer chromatography was run on pre-coated silica gel on aluminium plates obtained from Whatmann Inc. All the reactions were performed at 20 ºC. Büchi B-540 apparatus was used to obtain the melting points of all solid compounds. Bruker. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 400 and 100 MHz spectrometer respectively, chemical shifts were reported in (ppm) with TMS as internal standard. Elemental analyses were performed on Perkin Elmer – 2004. Quantity of all products reported are purified ones by column chromatography using 70–230 mesh silica gel.

Magnetic Reactor

The experimental setup is made up of a 1.1 kW three-phase induction motor having a stator winding of internal thickness and height of 14.39 X 160 mm, a rotor modified to hold an open-top toroidal cleaning chamber made from perspex plastic (internal, external and height diameters of 66 x 100 x 25 mm), a 10 A variable power source used as an AC power supply to the three-phase induction motor and a 220 V, 34 W fan mounted on a retort stand to maintain a uniform temperature within the system. Rotating magnetic field generated in the air-gap by the stator windings was measured using a digital gaussmeter (GM07/GM08 model), with a maximum magnetic field of 26.94 mT generated. The graphics representation of the magnetic reactor used to generate the magnetic field experimental setup is shown in figure 2.

Results and Discussion

As part of our ongoing project, we were demonstrating enzymatic catalysis under the influence of rotating magnetic field. The reaction mixture was static as the enzymes couldn't be moved around and to achieve the movement, enzymes were conjugated with carboxy functionalized polystyrene magnetic microspheres and brought the reaction mixture to stirring. When the control experiments were run, to our surprise, there was catalytic influence even without enzymes but with carboxy functionalized polystyrene magnetic microspheres. There were reports in the literature that, magnetic field can improve the catalytic activity thereby facilitating organic and biochemical reactions[34]. Surprised by these observations, in continuation of our interest in exploring catalyzing organic [3+2] cycloaddition reaction, we wanted to utilize this system for the [3+2] cycloaddition reaction. 150 mg of (2-nitroethenyl)benzene (1.0 mmol) is taken into the reactor, 5 mL of DMF and 155 mg of phenyl azide (1.3 equiv.) were charged and 50 μL Zepto™ magnetic ultra-blue carboxyl microspheres were added. The system was exposed to the magnetic field and reaction was monitored by TLC. After 6 hours, the disappearance of starting material (2-Nitroethenyl)benzene was observed on thin-layer chromatography. The reaction mixture was transferred to a test tube, centrifuged to separate the catalyst, the solvent was evaporated off under reduced pressure to get the crude product which was purified by column chromatography over silica gel using [ethyl acetate: hexane (1.5: 8.5)] as an eluent to afford 170 mg (85% yield) of pure 1,5-diphenyl-1*H*-1,2,3-triazole as white solid which melted at 113−114 °C (lit. 113−114 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.47−7.41 (m, 3H), 7.40−7.32 (m, 5H), 7.24−7.21 (m,

2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 136.6, 133.4, 129.4, 129.2, 128.9, 128.6, 126.8, 125.2 ppm. Further to standardize the reaction, (2-nitroethenyl)benzene with phenyl azide was carried out with various amounts of catalyst under varied time of magnetic exposure and the results are presented in table 1. It is very clear from table 1 that, 1 mM of (2-nitroethenyl)benzene, the catalyst required to afford the maximum yield (94%) is 250 μL of carboxy functionalized polystyrene magnetic microspheres and the maximum exposure time of magnetic field required is 180 minutes. To check with various other solvents, the reactions have been tried with EtOH, MeOH, 50% aqueous MeOH, THF, 50% aqueous THF, $CHCl_3$, CCl_4, CH_3NO_2, DMF and acetonitrile have been studied and among all, DMF emerged as the best solvent in terms of shorter reaction time and best yields and the next best solvent was DMSO which are presented in table 2. Encouraged by this result we wanted to investigate the reaction with other substituted nitroolefins such as phenyl and thio-nitroolefins with phenyl/benzyl azides for the suitability. The approach was successful, and the reactions afforded the expected 1,5-disubstituted-1,2,3-triazoles as products in high to excellent yields as shown in scheme 1 and the results are summarized in table 3. It is to be noted that, reaction of 4-nitro(2-nitroethenyl)benzene with benzyl azide gave the corresponding triazoline [1-Benzyl-5-(4-nitrophenyl)-1*H*-1,2,3-triazole, **3g**] in highest yield, almost quantitative, 99% whereas the reaction of 4-cyzno(2-nitroethenyl)benzene with benzyl azide gave the corresponding triazoline [4-(1-Benzyl-1*H*-1,2,3-triazol-5-yl)Benzonitrile, **3j**] in lowest yield, 60% with this system.

Control Experiment

The control experiments were run, firstly in the absence of magnetic field, but only using the catalyst Zepto^{TM} magnetic ultra-blue carboxyl microspheres under same reaction conditions, but using stirrer; secondly, under the magnetic field with no catalyst. There was no reaction even after 8 hours, in the latter case whereas trace products have seen on TLC in former case clearly indicating magnetic field is influencing the catalytic activity of Zepto^{TM} magnetic ultra-blue carboxyl microspheres to have catalytic activity which is catalyzing the [3+2] cycloaddition reaction of nitroolefins and azides to afford 1,5-disubstituted-1,2,3-triazolines. The control experiments were also carried to know the effect of rotation frequency for the reaction under the magnetic field, but we couldn't observe any difference with the rate of the reaction at varied rotation frequencies under the magnetic field strength 18.99 T. Further, the combined effect of

magnetic field and viscosity of the reaction mass have also been studied for any possible effect on the rate of reaction, but there was no significant contribution of viscosity of the reaction mixture. The plausible mechanism for the catalysis of carboxy functionalized Zepto magnetic microspheres for the 3+2 cycloaddition reaction is presented in below scheme 2.

Recycling the catalyst

On completion of the reaction, the reaction mixture along with solvent was taken into the test tube (15 mL capacity) and centrifuged, the liquid was decanted off and the catalyst (Zepto™ carboxy functionalized polystyrene magnetic fluorescent ultra-blue microspheres) stuck to the bottom of the test tube was added 5 mL of acetonitrile, heated to 40°C on a steam bath and centrifuged, the process was repeated twice and the recovered catalyst was utilized for fifteen subsequent reactions without any loss in catalytic activity.

General Procedure for the synthesis of 1,5-disubstituted-1,2,3-triazoles under the influence of rotating magnetic field

In to the reactor, a mixture of (2-nitroethenyl)benzene (1.0 mmol), DMF (5 mL) and phenyl/benzyl azide (1.3 equiv.)and Zepto™ carboxy functionalized polystyrene magnetic fluorescent ultra-blue microspheres (250 μL) were added. The reaction mixture was exposed to magnetic field at 20 °C. After completion of the reaction, the reaction mixture was transferred to a test tube, centrifuged to recover the catalyst. The filtrate was evaporated to dryness under vacuum to afford the crude which was purified by column chromatography using (1.5:8.5 :: ethyl acetate: hexane) as an eluent to afford pure 1,5-diphenyl-1*H*-1,2,3-triazole.

Conclusions

In summary, we have demonstrated the use of magnetic field in catalysing the 3+2 cyclo-addition of nitroolefins and azides to obtain a variety of 1,5-disubstituted-1,2,3-triazoles utilising carboxy functionalized magnetic microspheres as catalyst. The process is advantageous over the previous reports in terms reaction time, yields, no generation of undesired intermediates as the reactions were carried out at ambient temperature and the catalyst used is not complex material which would not generate any other inorganic complex which can easily separate by simple centrifugation which could be reused for the next subsequent reactions which makes the process neat and environmental friendly.

Supplementary data

Supplementary data are available with the article through the journal website.

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TABLES

Table 1. Standardization of the reaction of (2-nitroethenyl)benzene(1.0 mM) with phenyl azide(1.3 equiv.) with various amounts of catalyst Zepto™ magnetic ultra-blue carboxyl microspheres and varied time of magnetic exposure at 20 °C using DMF as solvent

Entry	Catalyst (μL)	Magnetic exposure (min)	Yield (%)
a	0	240	No reaction
b	5	240	Trace
c	10	240	5
d	15	240	8
e	20	240	14
f	25	240	20
g	30	240	26
h	35	240	35
i	40	240	52
j	45	240	66
k	50	240	83
l	55	240	85
m	60	180	85
n	75	180	85
o	100	180	90
p	125	180	93
q	200	180	94
r	250	180	94
s	300	180	94

Table 2. Standardization of the reaction of (2-nitroethenyl)benzene(1.0 mM) with phenyl azide(1.3 equiv.) employing Zepto™ magnetic ultra-blue carboxyl microspheres with various solvents.

Entry	Solvent	Reaction time (h)	Yield (%)
a	Hexane	4	No reaction
b	Ethylene glycol	4	No reaction
c	MeOH	4	12
d	50% aq MeOH	4	Trace
e	EtOH	4	9
f	50% aq EtOH	4	Trace
g	THF	4	18
h	50% aq THF	4	15
i	DMSO	4	85
j	DMF	3	94
k	$CHCl_3$	4	37
l	CCl_4	4	42
m	CH_3CN	4	32
n	CH_3NO_2	4	45

Table 3: Synthesis of 1,5-disubstituted-1,2,3-triazoles by the reaction of nitroolefins(1.0 mM) and (1.3 equiv.) catalyzed by Zepto™ magnetic ultra-blue carboxyl microspheres (250 μL) under the influence of rotating magnetic field using DMF as solvent.

Entry	R_1	R_2	Reaction time (min)	Yield (%)
a	H	Phenyl	180	94
b	4-NO2	Phenyl	210	88
c	4-Br	Phenyl	210	93
d	4-OCH3	Phenyl	210	87
e	Thiophene	Phenyl	180	82
f	H	Benzyl	240	92
g	4-NO_2	Benzyl	210	99
h	2-NO_2	Benzyl	210	96
i	2-Cl	Benzyl	210	98
j	4-CN	Benzyl	210	60
k	4-CH_3	Benzyl	240	92
l	4-OCH_3	Benzyl	240	95
m	4-OH	Benzyl	240	82
n	Thiophene	Benzyl	240	88

Captions to the figures

Figure 1.

Potential applications based on 1,5-disubstituted-1,2,3-triazoles

Figure 2.

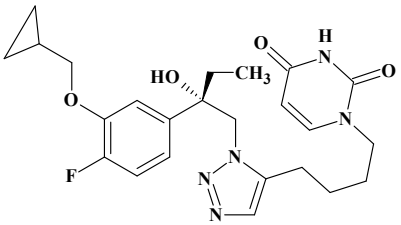
Graphical representation of the magnetic reactor used to generate the magnetic field

Scheme 1.

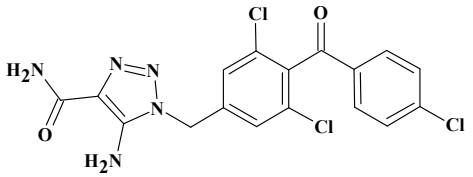
Cycloaddition reaction between nitrolefins and aryl/alkyl azides under the influence of magnetic field catalysed by magnetic microspheres

Scheme 2.

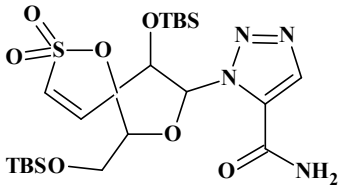
Plausible mechanism for the 3+2 cycloaddition nitrolefins and azides catalysed by carboxy functionalized magnetic microspheres



Potent Human DuTpase inhibitor
IC_{50} = 0.067 micromoles

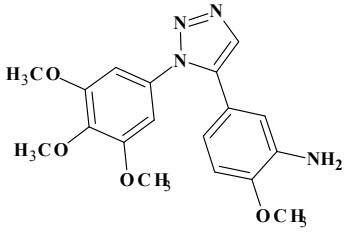


Active anticancer drug
Carboxyamidotriazole (CAI)

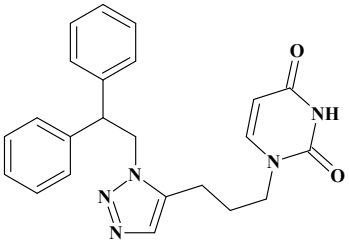


Non nucleoside reverse transcriptase inhibitor

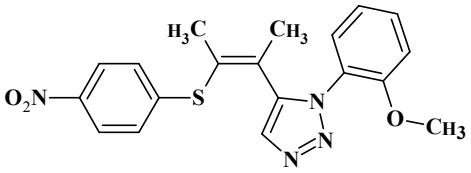
TSAO



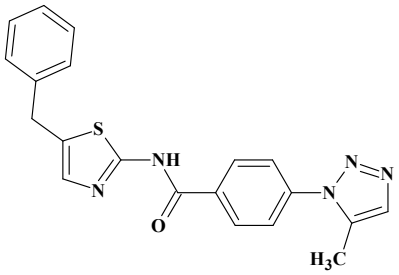
Tubulin polymerization inhibitor



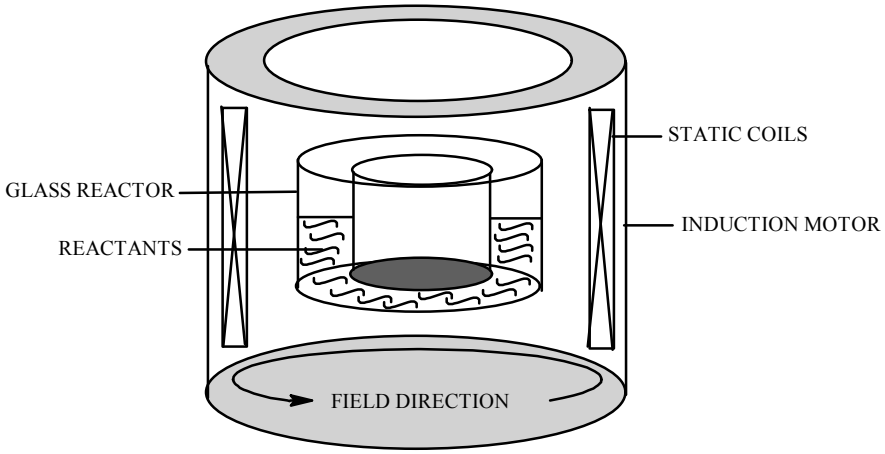
Potent Human DuTpase inhibitor
IC_{50} = 1.3 micromoles

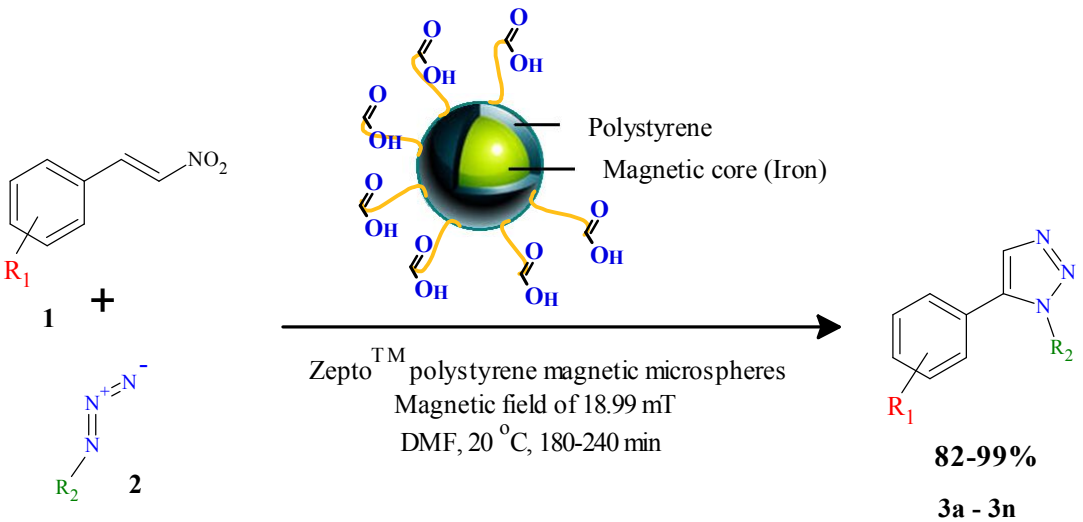


Potent HIV 1 Vif antagonist



High active on Leukemia & Melanoma





R_1 = H, CH_3, OCH_3, OH, NO_2, CN, Cl, Br, Thiophene;

R_2 = phenyl / benzyl group