Communication

Efficient Erbium-Catalyzed [3+2] Cycloaddition: Regioselective Synthesis of 1,5-Disubstituted 1,2,3-Triazoles

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Abstract: A simple procedure to obtain 1,5-disubstituted 1,2,3-triazoles, using the catalytic system erbium(III) trifluoromethanesulfonate, 1-methyl pyridinium trifluoromethanesulfonate and water is described. The reaction proceeds through an eliminative azide–olefin cycloaddition (EAOC) offering a highly regioselective approach and good yields (81–94%). The advantages of this method include simple operations of work-up and the ability of the catalytic system to be re-used five times without an evident loss in yield.

Keywords: triazoles, azides; 1,3-dipolar cycloaddition; EAOC.

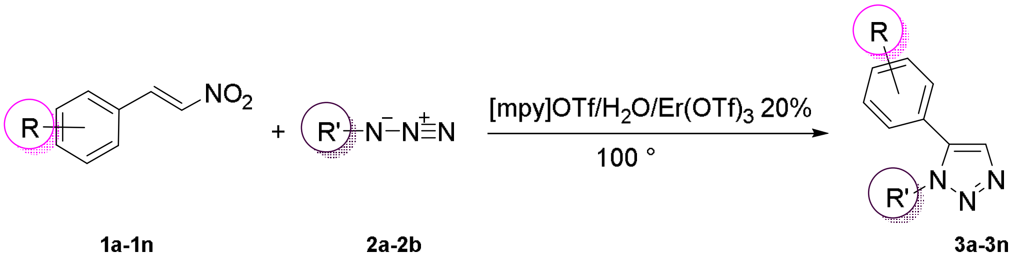
1. Introduction

The 1,2,3-triazole nucleus represents a significant class of biologically active nitrogen compounds that exhibit a number of important biological properties, such as antibacterial, anticancer, antivirus, and antituberculosis. [1,2] Moreover, 1,2,3-triazoles have found industrial applications as dyes, agrochemicals, corrosion inhibitors, and photostabilizers.[3,4] For the synthesis of 1,2,3-triazoles the classic approach mainly used is the 1,3-dipolar cycloaddition between substrates that contain triple bonds with organic azides. [5] In general, the most recent methods for the synthesis of heterocyclic compounds or their precursors are based on the use of catalysts like Lewis acids and/or non-conventional conditions (MW, ILs, DES, etc.) [6-13] Therefore, more recently, in order to develop regioselective triazole synthesis were used copper (CuAAC) or ruthenium (RuAAC) catalysts, obtaining 1,4- or 1,5-regioisomers, respectively. [14-17] Lewis acids like lanthanide triflates [18-21] are mild reagents, recoverable, and reusable and, thus, environmentally friendly. Lanthanide triflates seem to be very effective as catalysts in many organic reactions and in particular in 1,3-dipolar cycloaddition reactions. [22,23] Particularly, the system $Er(OTf)_3$/Ionic Liquid/H_2O used to catalyze Diels Alder reactions has emerged as a versatile tool for developing synthesis due to their numerous advantages, namely, their relatively high efficiency, water compatibility, mild reaction conditions, and eco-friendly catalytic reactions.[24] The merits of these systems derive from the rare-earth metal peculiar photophysical (in particular catalytic) properties [25] and from the dynamical processes of ionic liquids (emulated recently by ionic liquid – like systems) which, when simultaneously present, give synergic effects [26-28].

An alternative procedure to prepare 1,5-substituted triazoles is represented by eliminative azide–olefin cycloaddition (EAOC), in which azides are employed as dipole and electron deficient olefins are proposed to replace alkynes as dipolarophile. [29,30] The azide–olefin cycloaddition furnishes triazoline, an unstable compound that readily decompose but that may be transformed into the stable triazole by eliminative azide–olefin cycloaddition (EAOC). In particular, nitroolefins are revealed as excellent starting materials because of the presence of electron withdrawing nitro group both improves the 1,3-dipolar cycloaddition process, lowering the LUMO of the dipolarophile, and favors the formation of required 1,2,3-triazoles due to the fast nitrous acid loss through elimination step.[31]

2. Results and Discussion

Herein, we report a new synthetic method for 1,5 disubstituted 1,2,3-triazoles formation obtained by [3+2] cycloaddition of azides with electron-deficient dipolarophiles catalyzed by the $Er(OTf)_3/IL/H_2O$ system (Scheme 1).



Scheme 1. Generic reaction to synthesize 1,5-disubstituted 1,2,3-triazole

Initially, we commenced the reaction with ω-nitrostyrene **1a** (R = H) and phenylazide **2a** (R′ = Ph) as model substrates (Table 1).

Table 1. Optimization of reaction conditions for preparing 1,5 disubstituted 1,2,3-triazoles[1]

Entry	Catalyst	IL	Time (h)	Yield (%)	Product
1	none	[mpy]OTf	48	18	**3a**[b]
2	AgOTf (10%)	[mpy]OTf	3	20	**3a**
3	$Zn(OTf)_2$ (10%)	[mpy]OTf	3	34	**3a**
4[2]	$Cu(OTf)_2$ (10%)	[mpy]OTf	3	29	**3a**
5	$Sc(OTf)_3$ (10%)	[mpy]OTf	3	13	**3a**
6	$Ce(OTf)_3$ (10%)	[mpy]OTf	3	82	**3a**
7	$Er(OTf)_3$ (10%)	[mpy]OTf	3	91	**3a**
8	$Er(OTf)_3$ (10%)	[mpy]OTf	3	55	**3a**
9	$Er(OTf)_3$ (5%)	[mpy]OTf	6	78	**3a**
10	$Er(OTf)_3$ (10%)	[bmim]Cl	3	66	**3a**
11	$Er(OTf)_3$ (10%)	$[bmim]BF_4$	3	71	**3a**

[1] Reaction conditions: 2.0 eq. of **2a** were used unless the reaction in entry 8, in which 1.0 eq. of **2a** was employed. 100 μl of water was added to 5 ml of ionic liquid (IL/H_2O v/v 5:0.1).

[2] A mixture of 1,4- and 1,5-disubstituted 1,2,3-triazoles was observed.

We decided to explore prevalently 1-methyl pyridinium trifluoromethanesulfonate [mpy]OTf as ionic liquid for its easy one-step preparation through halide-free direct synthesis, by adding directly methyltrifluoromethanesulfonate to dry pyridine.[32] Moreover, triflate salts were only employed to avoid the simultaneous presence of different counteranions in the reaction system. Without any catalyst, a mixture of 1,4- and 1,5-disubstituted triazoles were observed in very low yield after a long reaction time (entry 1, Table 1). Exploring between a number of triflate salts (entry 2-7,table 1) we found that the $Er(OTf)_3$ was the most effective, carrying out the desired product in very high yield (entry 7, table 1). Halving the amount of reagent **2a** only a 55% of **3a** was obtained (entry 8, table 1), whereas, when the catalyst was decreased to 5 mol % (entry 9, table 1) the yield of final product was lower than that obtained using 10 mol% of catalyst. Additional experiments with different ionic liquids (entry 10-11, table 1), confirmed that the [mpy]OTf appeared to be the best choice. Probably, it may due to increased solvation of dipolarophile intermediate because of higher charge localization in piridynium cation than imidazolim cation. [33]

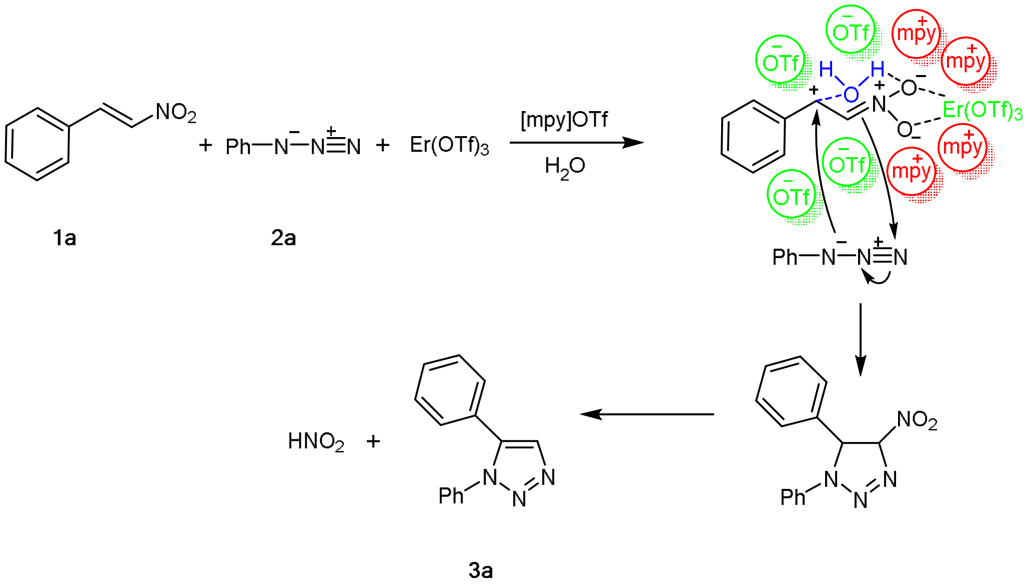
Using our optimized experimental conditions, we investigated the reaction of various arylnitroolefins **1a-1n** and phenylazide **2a** or benzylazide **2b** (Table 2).

Table 2. Preparation of 1,5-dsubstituted 1,2,3-triazoles **3a-3n**

Entry	R	R^1	Product	Yield (%)
1	H	Ph	**3a**	90
2	4-Me	Ph	**3b**	94
3	4-MeO	Ph	**3c**	91
4	2-NO_2	Ph	**3d**	88
5	2-Cl	Ph	**3e**	81
6	3-Cl	Ph	**3f**	85
7	4-Cl	Ph	**3g**	90
8	H	Bn	**3h**	91
9	4-Me	Bn	**3i**	90
10	4-MeO	Bn	**3j**	92
11	2-NO_2	Bn	**3k**	86
12	2-Cl	Bn	**3l**	81
13	3-Cl	Bn	**3m**	80
14	4-Cl	Bn	**3n**	85

It is to note that nitroolefins bearing electron-withdrawing and electron-donors substituents were used as starting materials without observing considerable variations in the reaction path. Furthermore, in all cases, it is good to highlight that the intermediate triazoline has never been isolated because it spontaneously evolves to the corresponding triazole by loss of HNO_2.

At this point, we propose a possible reaction mechanism for the reaction of **1a** with **2a** as illustrated in Scheme 2.



Scheme 2. Proposed mechanism to formation of 1,5-disubstituted 1,2,3-triazoles.

The first step of the reaction may be represented by the coordination of erbium(III) triflate to nitroolefin compound **1a** to form an activated intermediate stabilized through hydrogen bonds with water and electrostatic interactions with the cation and the anion of ionic liquid. Then, the solvated intermediate reacts with the azide derivative **2a** by a 1,3-dipolar cycloaddition reaction to form a triazoline substrate that evolves to the 1,5-disubstituted 1,2,3-triazole **3a** *via* a step of elimination of

HNO_2. The catalytic system [mpy]OTf/Er(TfO)$_3$ has been analyzed with respect recovery and re-use in the reaction between ω-nitrostyrene **1a** and benzylazide **2a** and the results are shown in Table 3.

Table 3. Recovery and re-use of catalytic [mpy]OTf/Er(OTf)$_3$ system until six cycles

Entry	Cycle	Yield (%)
1	0	91
2	1	91
3	2	90
4	3	90
5	4	89
6	5	88

The results of table 3 demonstrate that the [mpy]OTf/H_2O/Er(OTf)$_3$ system remains active until six cycles without loss of efficiency.

3. Materials and Methods

All chemicals purchased from common commercial sources were used as received without any further purification. Reactions were monitored by TLC using silica plates 60-F264, commercially available from Merck. ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively, in $CDCl_3$ using tetramethylsilane (TMS) as internal standard (Bruker ACP 300 MHz). Chemical shifts are given in parts per million and coupling constants in Hertz. LC-MS analysis were carried using an Agilent 6540 UHD Accurate - Mass Q-TOF LC-MS (Agilent, Santa Clara, CA) fitted with a electrospray ionization source (Dual AJS ESI) operating in positive ion mode. Chromatographic separation was achieved using a C18 RP analytical column (Poroshell 120, SB-C18, 50 x 2.1 mm, 2.7 mm) at 30 °C with a elution gradient from 5% to 95% of B over 13 min., a being H_2O (0.1% FA) and B CH_3CN (0.1% FA). Flow rate was 0.4 mL min^{-1}.

Synthesis of Ionic Liquids

1-Methyl pyridinium trifluoromethanesulfonate ([mpy]OTf) was prepared by halide-free direct synthesis in according to the procedure reported in the literature. [24,34]

Recycling of the catalytic system IL/FeCl$_3$

After the polar phase was extracted three times by dichloromethane, the ionic liquid/H_2O/Er(OTf)$_3$ system was washed with hexane and dried under vacuum condition. Successive runs were performed in the recycled catalytic system by reacting fresh reagents at the usual conditions.

*General procedure for synthesis of 1,5-disubstituted-1,2,3-triazoles **3a-3n***

In a two-necked round bottom flask, equipped with bubble condenser and magnetic stir bar, ionic liquid (5ml), water (0.1 ml), Er(OTf)$_3$ (20 mol%), (*E*)-nitrostyrene **1a-1n** (1 eq) and azide **2a-2b** (2 eq) were placed. The reaction was conducted at 100°C for the appropriate time. The crude was extracted with dichloromethane (3x5ml) and the combined organic layer was evaporated under vacuum. The crude product was purified on flash silica gel column by using hexane/ethyl acetate (9:1 v/v) to obtain the desired product (**3a-3n**).

*1,5-diphenyl-1,2,3-triazole (**3a**).* Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.22-7.31 (m, 2H, Ar), 7.36-7.44 (m, 5H, Ar), 7.44-7.50 (m, 3H, Ar),7.90 (s, 1H, CH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 125.23, 126.79, 128.61, 128.87, 129.24, 129.37, 133.41, 136.64, 137.75. ESI(+)-MS: *m/z* [M+H] calcd for $C_{14}H_{12}N_3$ 222.1026, found: 222.0591.

*5-(4-methylphenyl)-1-phenyl-1,2,3-triazole (**3b**)* Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 2.36 (s, 3H, CH_3), 7.08-7.18 (m, 4H, Ar), 7.33-7.41 (m, 2H, Ar), 7.41-7.48 (m, 3H, Ar),7.84 (s, 1H, CH);

^{13}C NMR (CDCl$_3$, 75 MHz): δ (ppm) 21.30, 116.82, 123.74, 125.25, 128.47, 129.21, 129.58, 133.14, 137.89, 139.42. ESI(+)-MS: *m/z* [M+H] calcd for C$_{15}$H$_{14}$N$_3$ 236.1182, found: 236.0834.

*5-(4-methoxyphenyl)-1-phenyl-1,2,3-triazole (**3c**).* Yellow oil. ^{1}H NMR (CDCl$_3$, 300 MHz): δ (ppm) 3.81 (s, 3H, CH$_3$), 6.83-6.90 (m, 2H, Ar), 7.10-7.18 (m, 2H, Ar), 7.34-7.41 (m, 2H, Ar),7.41-7.48 (m, 3H, Ar), 7.81 (s, 1H, CH); ^{13}C NMR (CDCl$_3$, 75 MHz): δ (ppm) 55.32, 114.35, 118.95, 125.24, 129.14, 129.35, 129.96, 132.96, 136.76, 137.60, 160.28. ESI(+)-MS: *m/z* [M+H] calcd for C$_{15}$H$_{14}$N$_3$O 252.1131, found: 252.1197.

*5-(2-nitrophenyl)-1-phenyl-1,2,3-triazole (**3d**).* Colorless oil. ^{1}H NMR (CDCl$_3$, 300 MHz): δ (ppm) 7.28-7.31 (m, 1H, Ar), 7.33-7.42 (m, 3H, Ar), 7.46 (dd, 1H, J=7.42 Hz, 1.70 Hz, Ar), 7.60-7.75 (m, 3H, Ar), 7.84 (s, 1H, CH), 8.04 (dd, 1H, J=7.90 Hz, 1.60 Hz, Ar); ^{13}C NMR (CDCl$_3$, 75 MHz): δ (ppm) 122.56, 124.53, 125.17, 129.38, 129.46, 130.92, 132.78, 133.45, 133.75, 135.94, 148.34. ESI(+)-MS: *m/z* [M+H] calcd for C$_{14}$H$_{11}$N$_4$O$_2$ 267.0877, found: 267.1267.

*5-(2-chlorophenyl)-1-phenyl-1,2,3-triazole (**3e**).* Colorless oil. ^{1}H NMR (CDCl$_3$, 300 MHz): δ (ppm) 7.22-7.32 (m, 2H, Ar), 7.32-7.43 (m, 6H, Ar), 7.43-7.50 (m, 1H, Ar),7.90 (s, 1H, CH); ^{13}C NMR (CDCl$_3$, 75 MHz): δ (ppm) 124.16, 126.60, 127.02, 129.02, 129.26, 130.22, 131.07, 131.95, 134.13, 134.75, 134.90, 136.62. ESI(+)-MS: *m/z* [M+H] calcd for C$_{14}$H$_{11}$ClN$_3$ 256.0636, found: 256.0782.

*5-(3-chlorophenyl)-1-phenyl-1,2,3-triazole (**3f**).* Colorless oil. ^{1}H NMR (CDCl$_3$, 300 MHz): δ (ppm) 7.06-7.13 (m, 1H, Ar), 7.26-7.35 (m, 2H, Ar), 7.35-7.44 (m, 3H, Ar), 7.45-7.55 (m, 3H, Ar), 7.92 (s, 1H, CH); ^{13}C NMR (CDCl$_3$, 75 MHz): δ (ppm) 125.21, 126.73, 128.57, 129.39, 129.53, 129.55, 130.14, 133.64, 134.89, 136.28, 136.42. ESI(+)-MS: *m/z* [M+H] calcd for C$_{14}$H$_{11}$ClN$_3$ 256.0636, found: 256.0781.

*5-(4-chlorophenyl)-1-phenyl-1,2,3-triazole (**3g**).* Yellow oil. ^{1}H NMR (CDCl$_3$, 300 MHz): δ (ppm) 7.13-7.20 (m, 2H, Ar), 7.30-7.39 (m, 4H, Ar), 7.43-7.50 (m, 3H, Ar),7.87 (s, 1H, CH); ^{13}C NMR (CDCl$_3$, 75 MHz): δ (ppm) 125.23, 129.23, 129.47, 129.52, 129.83, 133.45, 135.51, 136.38, 136.68. ESI(+)-MS: *m/z* [M+H] calcd for C$_{14}$H$_{11}$ClN$_3$ 256.0636, found: 256.0781.

*1-benzyl-5-phenyl-1,2,3-triazole (**3h**).* Colorless oil. ^{1}H-NMR (CDCl$_3$, 300 MHz): δ (ppm) 5.55 (s, 2H, CH$_2$), 7.05-7.12 (m, 2H, Ar), 7.22-7.33 (m, 5H, Ar), 7.38-7.48 (m, 3H, Ar), 7.75 (s, 1H, CH). ^{13}C-NMR (CDCl$_3$, 75 MHz): δ (ppm) 51.83, 126.97, 127.17, 128.16, 128.82, 128.92, 128.95, 129.50, 133.30, 135.53, 138.15. ESI(+)-MS: *m/z* [M+H] calcd for C$_{15}$H$_{14}$N$_3$ 236.1182, found: 236.0952.

*1-benzyl-5-(4-methylphenyl)-1,2,3-triazole (**3i**).* Colorless oil. ^{1}H NMR (CDCl$_3$, 300 MHz): δ (ppm) 2.43 (s, 3H, CH$_3$), 5.57 (s, 2H, CH$_2$), 7.09-7.22 (m, 4H, Ar), 7.22-7.29 (m, 2H, Ar), 7.29-7.37 (m, 3H, Ar), 7.75 (s, 1H, CH); ^{13}C NMR (CDCl$_3$, 75 MHz): δ (ppm) 21.31, 51.71, 123.94, 128.10, 128.76, 128.81, 129.64, 133.16, 135.67, 139.63. ESI(+)-MS: *m/z* [M+H] calcd for C$_{16}$H$_{16}$N$_3$ 250.1339, found: 250.1241

*1-benzyl-5-(4-methoxyphenyl)-1,2,3-triazole (**3j**).* Yellow oil. ^{1}H NMR (CDCl$_3$, 300 MHz): δ (ppm) 3.87 (s, 3H, CH$_3$), 5.56 (s, 2H, CH$_2$), 6.92-6.99 (m, 2H, Ar), 7.08-7.16 (m, 2H, Ar), 7.17-7.24 (m, 2H, Ar), 7.28-7.37 (m, 3H, Ar), 7.73 (s, 1H, CH); ^{13}C NMR (CDCl$_3$, 75 MHz): δ (ppm) 51.67, 55.39, 114.42, 119.01, 127.12, 128.12, 128.84, 130.25, 133.09, 135.69, 137.99, 160.52. ESI(+)-MS: *m/z* [M+H] calcd for C$_{16}$H$_{16}$N$_3$O 266.1288, found: 266.1609.

*1-benzyl-5-(2-nitrophenyl)-1,2,3-triazole (**3k**).* Colorless oil. ^{1}H NMR (CDCl$_3$, 300 MHz): δ (ppm) 5.42 (s, 2H, CH$_2$), 6.90-6.97 (m, 2H, Ar), 7.00 (dd, 1H, J=7.50Hz, 1.53Hz, Ar), 7.15-7.25 (m, 3H, Ar), 7.55 (td, 1H, J=7.54Hz, 1.56Hz, Ar), 7.62 (dd, 1H, J= 7.95 Hz, 1.56Hz, Ar), 7.66 (s, 1H, CH),8.12 (dd, 1H, J=8.21Hz, 1.43Hz, Ar);^{13}C NMR (CDCl$_3$, 75 MHz): δ (ppm) 52.85, 122.27, 124.92, 127.77, 128.42, 128.72, 131.01, 133.04, 133.11, 133.23, 133.94, 134.40. ESI(+)-MS: *m/z* [M+H] calcd for C$_{15}$H$_{13}$N$_4$O$_2$ 281.1033, found: 281.1016.

*1-benzyl-5-(2-chlorophenyl)-1,2,3-triazole (**3l**).* Colorless oil. ^{1}H-NMR (CDCl$_3$, 300 MHz): δ (ppm) 5.45 (s, 2H, CH$_2$), 6.90-6.99 (m, 2H, Ar), 7.01 (d, 1H, J=7.60 Hz, 1.70 Hz, Ar), 7.15-7.30 (m, 4H, Ar), 7.40 (td, 1H, J=7.70Hz, 1.70Hz, Ar), 7.47-7.52 (m, 1H, Ar), 7.72 (s, 1H, CH). ^{13}C-NMR (CDCl$_3$, 75 MHz): δ (ppm) 52.50, 126.44, 126.90, 127.72, 128.21, 128.62, 129.97, 131.18, 132.01, 134.32, 134.43, 134.78, 134.83. ESI(+)-MS: *m/z* [M+H] calcd for C$_{15}$H$_{13}$ClN$_3$ 270.0793, found: 270.1254.

*1-benzyl-5-(3-chlorophenyl)-1,2,3-triazole (**3m**).* Colorless oil. ^{1}H-NMR (CDCl$_3$, 300 MHz): δ (ppm) 5.55 (s, 2H, CH$_2$), 7.05-7.16 (m, 3H, Ar), 7.23 (m, 1H, Ar), 7.26-7.34 (m, 3H, Ar), 7.36 (d, 1H, J=7.55Hz, Ar), 7.39-7.45 (m, 1H, Ar), 7.75 (s, 1H, CH); ^{13}C-NMR (CDCl$_3$, 75 MHz): δ (ppm) 52.11, 127.03, 127.21, 128.37, 128.64, 128.94, 129.01, 129.66, 130.22, 133.52, 134.92, 135.18, 136.80. ESI(+)-MS: *m/z* [M+H] calcd for $C_{15}H_{13}ClN_3$ 270.0793, found: 270.1256.

*1-benzyl-5-(4-chlorophenyl)-1,2,3-triazole (**3n**).* Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 5.54 (s, 2H, CH_2), 7.03-7.10 (m, 2H, Ar), 7.14-7.21 (m, 2H, Ar), 7.25-7.33 (m, 3H, Ar), 7.36-7.43 (m, 2H, Ar), 7.74 (s, 1H, CH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 51.95, 125.37, 127.07, 128.31, 128.94, 129.26, 130.19, 133.46, 135.30, 135.85, 137.04. ESI(+)-MS: *m/z* [M+H] calcd for $C_{15}H_{13}ClN_3$ 270.0793, found: 270.1252.

4. Conclusions

In conclusion, we have realized an efficient route for the synthesis of 1,5-disubstitued-1,2,3-triazoles using an eco-friendly catalytic system formed by erbium(III) trifluoromethanesulfonate, 1-methyl pyridinium trifluoromethanesulfonate and water. The reactions proceed in a highly regioselective manner with the possibility to reuse of catalytic system until six cycles. This strategy has many advantages, for example high regioselectivity, good yields and experimentally convenient catalytic process, which could significantly direct further research of eco-friendly synthesis of 1,5-disubstituted triazoles.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1. ^{1}H NMR, 13C NMR and ESI(+)-MS spectra of . *1,5-diphenyl-1,2,3-triazole (**3a**), 5-(4-methylphenyl)-1-phenyl-1,2,3-triazole (**3b**), 5-(4-methoxyphenyl)-1-phenyl-1,2,3-triazole (**3c**), 5-(2-nitrophenyl)-1-phenyl-1,2,3-triazole (**3d**), 5-(2-chlorophenyl)-1-phenyl-1,2,3-triazole (**3e**), 5-(3-chlorophenyl)-1-phenyl-1,2,3-triazole (**3f**), 5-(4-chlorophenyl)-1-phenyl-1,2,3-triazole (**3g**), 1-benzyl-5-phenyl-1,2,3-triazole (**3h**), 1-benzyl-5-(4-methylphenyl)-1,2,3-triazole (**3i**), 1-benzyl-5-(4-methoxyphenyl)-1,2,3-triazole (**3j**), 1-benzyl-5-(2-nitrophenyl)-1,2,3-triazole (**3k**), 1-benzyl-5-(2-chlorophenyl)-1,2,3-triazole (**3l**), 1-benzyl-5-(3-chlorophenyl)-1,2,3-triazole (**3m**), 1-benzyl-5-(4-chlorophenyl)-1,2,3-triazole (**3n**).*

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