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PII: S0040-4039(16)30615-3
DOI: <http://dx.doi.org/10.1016/j.tetlet.2016.05.082>
Reference: TETL 47701

To appear in: *Tetrahedron Letters*

Received Date: 29 March 2016
Revised Date: 14 May 2016
Accepted Date: 21 May 2016



Please cite this article as: Singh, H., Khanna, G., Khurana, J.M., DBU catalyzed metal free synthesis of fused 1,2,3-triazoles through [3+2] cycloaddition of aryl azides with activated cyclic C-H acids, *Tetrahedron Letters* (2016), doi: <http://dx.doi.org/10.1016/j.tetlet.2016.05.082>

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DBU catalyzed metal free synthesis of fused 1,2,3-triazoles through [3+2] cycloaddition of aryl azides with activated cyclic C-H acids**Harjinder Singh, Garima Khanna and Jitender M. Khurana***

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Abstract

DBU catalyzed synthesis of fused 1,2,3-triazoles by [3+2] cycloaddition of aryl azides with activated cyclic C-H acids such as dimedone, cyclohexane-1,3-dione, 5-methylcyclohexane-1,3-dione and 2-hydroxynaphthalene-1,4-dione in PEG-400 has been reported under heating. The important features of this reaction are high yield products, short reaction times, easy availability of starting materials and recyclability of both reaction medium and catalyst.

Keywords

DBU, Triazoles, PEG-400, Cycloaddition

1,2,3-Triazoles represent an important class of biologically active nitrogen containing heterocyclic compounds with numerous biological activities such as, antibacterial, anticancer, antiviral, antiHIV, and antituberculosis.¹ Compounds containing 1,2,3-triazole ring fused with various carbocycles exhibited significant biological activities *e.g.* they act as benzodiazepine and adenosine receptors^{2,3}, γ -secretase modulator (GSM) for the treatment of Alzheimer's disease.⁴ Some of the biologically active compounds containing fused 1,2,3-triazole ring are shown in Figure 1.

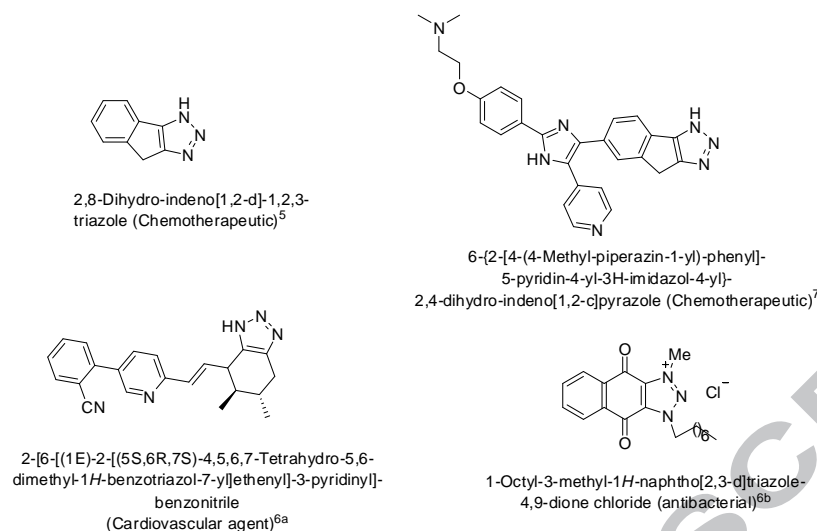


Figure 1: Examples of some biologically active fused 1,2,3-triazoles.

The Cu (I)-catalyzed azide–alkyne cycloaddition (CuAAC) has been extensively used for the synthesis of 1,4-disubstituted 1,2,3-triazoles with high regioselectivity and with huge implications in organic synthesis.⁸ Subsequently, the synthesis of 1,5-disubstituted 1,2,3-triazoles were achieved by the RuAAC reaction.⁹ Several other methods including the IrAAC reaction and Pd-catalyzed alkenyl bromide-azide cycloaddition have been developed for the regioselective synthesis of substituted triazoles.¹⁰⁻¹² All these reactions employ heavy metals as catalysts, which restrict their application in biological sciences. Moreover, these methods cannot be employed for the synthesis of fused 1,2,3-triazoles because of the non-availability of smaller cyclic alkynes as the smallest cyclic alkyne isolated is cyclooctyne and also because of their low reactivity. The metal free procedure for synthesis of substituted 1,2,3-triazoles such as enamine/dienamine-azide cycloaddition, enolate-azide cycloaddition, strained alkyne-azide cycloaddition¹³⁻¹⁶ have also been reported in literature, but have not been explored for the synthesis of fused 1,2,3-triazoles. Methods such as Pd-catalyzed cyclization of 5-iodotriazoles¹⁷, oxidative alcohol–azide cycloaddition¹⁸, cycloaddition of unactivated ketones/activated ketones to aryl azides^{19,20} for the

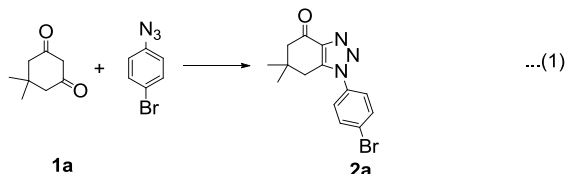
synthesis of fused 1,2,3-triazoles, have disadvantages such as poor yield of products, use of expensive catalyst, and volatile organic solvents, long reaction times, severe reaction conditions etc.

The development of new strategies to synthesize fused 1,2,3-triazoles is highly desirable in view of their importance. Therefore, in continuation of our research interest for the synthesis of variously substituted 1,2,3-triazoles²¹ and to investigate a novel methodology for the synthesis of fused 1,2,3-triazoles, we attempted reactions of aryl azides with cyclic C-H acids, using organobases (metal free conditions) in environmentally benign solvents like PEG-400.

In this paper, we wish to report for the first time the synthesis of fused 1,2,3-triazoles by cycloaddition of various aryl azides with cyclic 1,3-dicarbonyl compounds such as dimedone (1a), cyclohexane-1,3-dione (1b), 5-methylcyclohexane-1,3-dione (1c) and 2-hydroxy-1,4-naphthoquinone (1d) using catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in PEG-400 at 80 °C. Different aryl azides were prepared from corresponding aryl amines by reported procedure²².

The reaction conditions were optimized after attempting reactions of **1a** (1.0 mmol) with 4-bromophenyl azide (1.0 mmol) under different reaction conditions as listed in Table 1. Firstly, the model reaction was attempted using a catalytic amount of the tertiary amine base Et₃N (10 mol%) in PEG-400 at 80 °C. The reaction was complete after 240 min as indicated by TLC. After workup, the desired product 6,6-dimethyl-1-(4-bromophenyl)-6,7-dihydro-1*H*-benzo[*d*][1,2,3]triazol-4(5*H*)-one (2a) was obtained in 74% yield (eq. 1) (Entry 1, Table 1). The above reaction was then examined by using different nitrogenous organic base catalysts such as DABCO, DBU, pyrrolidine and piperidine (10 mol%) in PEG-400 at 80 °C (Entries 2-5, Table

1). Among all these bases, DBU was found to exhibit best catalytic activity as it gave the product **2a** in 89% yield after 60 min (Entry 3, Table 1) unlike other base catalysts which gave product **2a** in inferior yields and required longer reaction for completion (Entries 2-5 Table 1).



Therefore, we decided to attempt reactions with DBU in different solvents such as ethanol, DMSO, water and acetonitrile using DBU (10 mol%) as catalyst at 80 °C (Entries 6-9, Table 1). The reaction was incomplete when attempted in ethanol even after 240 min with 60% yield of desired product **2a** (Entry 6, Table 1). Reactions using DMSO, water, and acetonitrile as solvent required longer reaction times and gave inferior yields (Entries 7-9, Table 1) compared to PEG-400 (Entry 3, Table 1). The reaction of **1a** and 4-bromophenyl azide in PEG-400 was then attempted at lower temperature and also with lower catalyst loading. The reactions at lower temperature (60 °C) and with lower catalyst loading (5 mol%) resulted in increase in reaction time and decrease in product yield (Entries 10-11, Table 1).

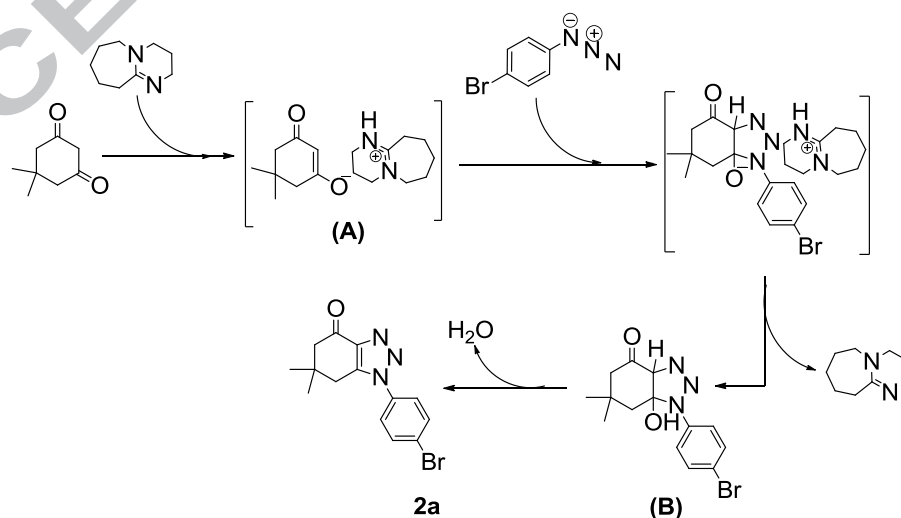
Table 1. Optimization of reaction conditions for synthesis of fused 1,2,3-triazoles by reaction of **1a** (1 mmol) with 4-bromophenylazide (1 mmol) under different conditions

Entry	Solvent	Base	Temp. (°C)	Time (min)	Yield (%)
1.	PEG-400	Et ₃ N (10 mol %)	80	240	74
2.	PEG-400	DABCO (10 mol%)	80	180	78
3.	PEG-400	DBU (10 mol%)	80	60	89
4.	PEG-400	Pyrrolidine (10 mol%)	80	180	76

5.	PEG-400	Piperidine (10 mol%)	80	180	72
6.	Ethanol	DBU (10 mol%)	80	240	60 ^a
7.	DMSO	DBU (10 mol%)	80	150	74
8.	Water	DBU (10 mol%)	80	180	79
9.	Acetonitrile	DBU (10 mol%)	80	120	80
10.	PEG-400	DBU (10 mol%)	60	90	82
11.	PEG-400	DBU (5 mol%)	80	90	79

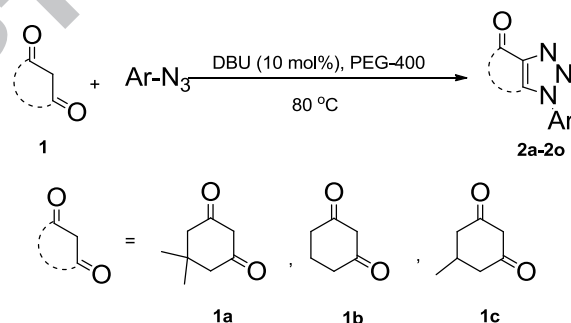
^a Incomplete reaction

It can be inferred from above results that reaction of dimedone and 4-bromophenyl azide gave the highest yield of the desired [3+2] cycloaddition product using DBU (10 mol%) as a base catalyst in PEG-400 at 80 °C. The probable mechanism of cycloaddition of dimedone and 4-bromophenyl azide in presence of DBU is shown in Scheme 1. Firstly, reaction of DBU with dimedone results in the formation of enolate (A), which undergoes 1,3-dipolar cycloaddition with 4-bromophenyl azide, leading to the formation of triazoline intermediate (B) and regeneration of DBU. This triazoline intermediate (B) undergoes elimination of water to give 6,6-dimethyl-1-(4-bromophenyl)-6,7-dihydro-1*H*-benzo[*d*][1,2,3]triazol-4(5*H*)-one (2a).



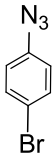
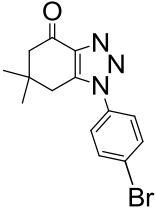
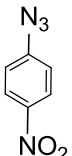
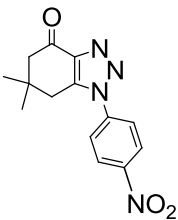
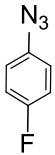
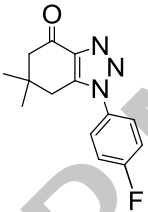
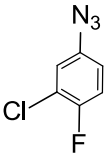
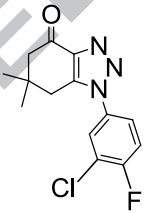
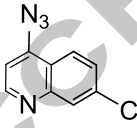
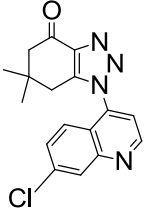
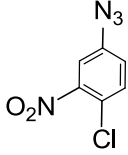
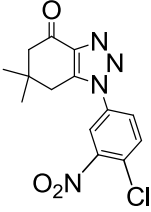
Scheme 1 Mechanism for synthesis of fused 1,2,3-triazole **2a** in presence of DBU as catalyst.

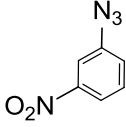
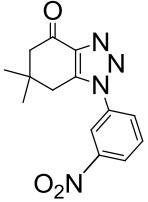
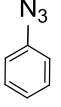
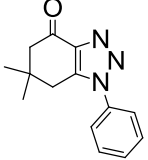
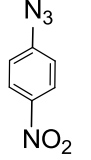
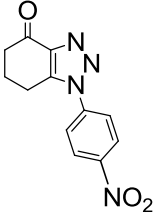
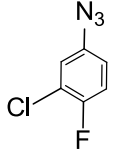
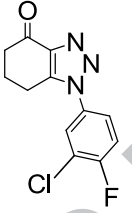
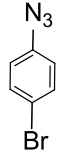
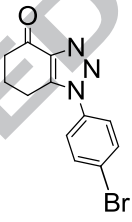
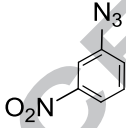
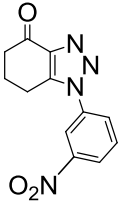
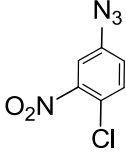
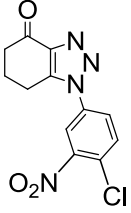
With the optimized reaction conditions in hand, the scope of this DBU catalyzed [3+2] cycloaddition reaction was further investigated. The reactions of different aryl azides (1 mmol) such as 4-nitrophenylazide, 4-fluorophenylazide, 4-fluoro-3-chlorophenylazide, 4-azido-7-chloroquinoline, 4-chloro-3-nitrophenyl azide, 3-nitrophenylazide and phenyl azide were carried out with **1a** (1.0 mmol) in PEG-400 using DBU (10 mol%) as catalyst at 80 °C. All the reactions proceeded smoothly and were complete in 20 min to 240 min yielding corresponding fused 1,2,3-triazoles *i.e.* 1-aryl-6,6-dimethyl-6,7-dihydro-1*H*-benzo[*d*][1,2,3]triazol-4(5*H*)-ones (**2b-2h**) in high yields (Entries 2- 8, Table 2, Scheme 1). Similarly the reaction of aryl azides (1.0 mmol) with **1b** (1.0 mmol) and **1c** (1.0 mmol) instead of **1a** under otherwise identical conditions gave corresponding 1-aryl-6,7-dihydro-1*H*-benzo[*d*][1,2,3]triazol-4(5*H*)-ones (**2i-2m**, Entries 9-13, Table 2) and 6-methyl-1-aryl-6,7-dihydro-1*H*-benzo[*d*][1,2,3]triazol-4(5*H*)-ones (**2n-2o**, Entries 14-15, Table 2)²⁴, respectively, in high yields. The generalized equation for cycloaddition is shown in Scheme 2.



Scheme 2: Synthesis of fused 1,2,3-triazoles (**2a-2o**).

Table 2. Synthesis of fused 1,2,3-triazoles (**2a-2o**)

S.No	ArN ₃	1	Product	Time (min)	Yield (%)
1.		1a		60	90
2.		1a		20	92
3.		1a		60	87
4.		1a		60	88
5.		1a		30	81
6.		1a		25	90

7.		1a		45	78 ^a
8.		1a		240	80
9.		1b		20	86
10.		1b		60	84
11.		1b		40	87
12.		1b		50	80 ^a
13.		1b		30	82

14.		1c		30	90
15.		1c		35	82

^aYield after column chromatography

The structures of all new products were confirmed by IR, ¹H NMR, ¹³C NMR and HRMS spectra. Structure of compound **2b** was further confirmed by single crystal X-ray crystallography. The single crystal X-ray structure of compound **2b** is shown in **Figure 2**.

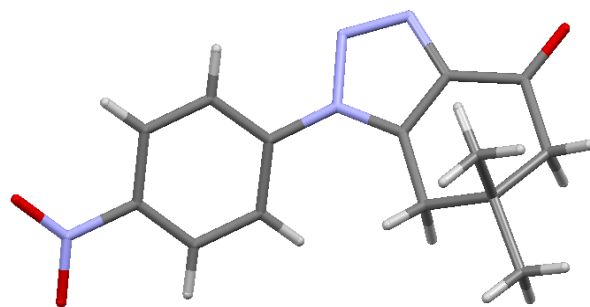
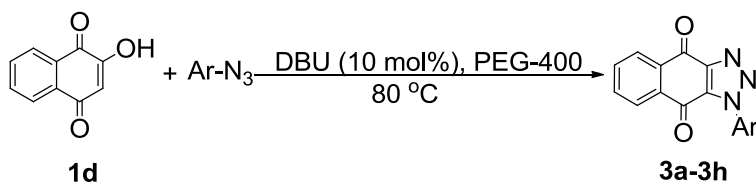


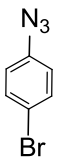
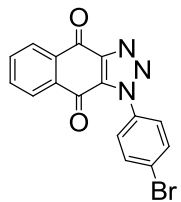
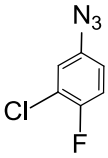
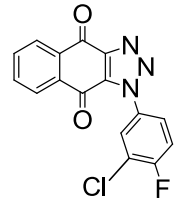
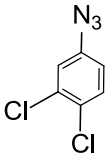
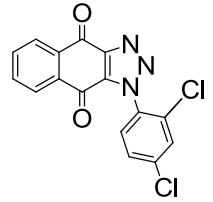
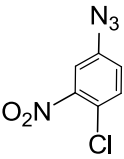
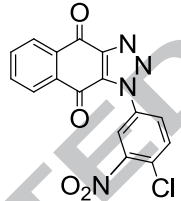
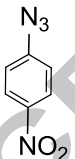
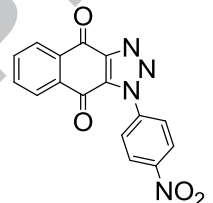
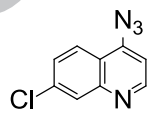
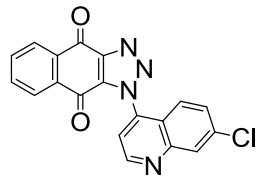
Figure 2: Single crystal X-ray structure of compound **2b** (CCDC No. 1452232)

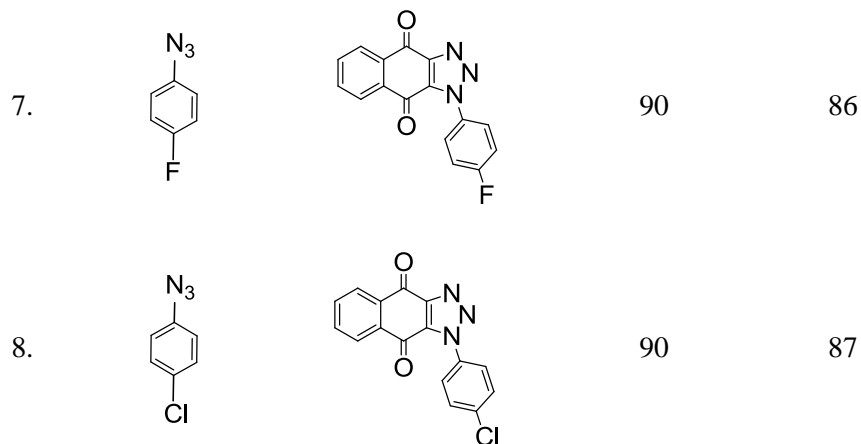
Subsequently activated cyclic C-H acid 2-hydroxynaphthalene-1,4-dione was also investigated for this cycloaddition reaction with various aryl azides. All the reactions proceeded smoothly and gave the desired products in good yields (Scheme 3) (entries 1-8, Table 3).



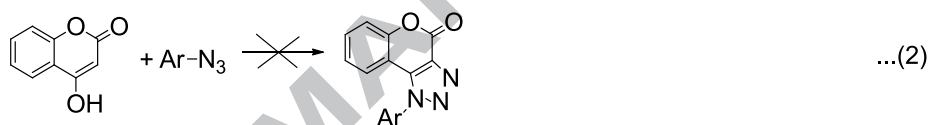
Scheme 3. Synthesis of 1-aryl-1H-naphtho[2,3-d][1,2,3]triazole-4,9-diones (**3a-3h**)

Table 3. Synthesis of 1-aryl-1*H*-naphtho[2,3-*d*][1,2,3]triazole-4,9-diones (**3a-3h**)

Entry	ArN ₃	Product	Time (Min)	Yield (%)
1.			90	81
2.			60	86
3.			45	81
4.			30	87
5.			45	86
6.			90	83



All our efforts to prepare fused triazoles with 4-hydroxycoumarin under a variety of conditions were unsuccessful (eq. 2).

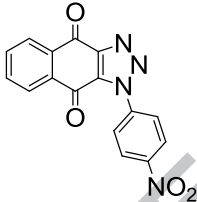
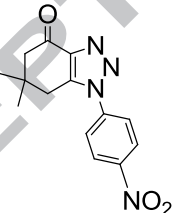
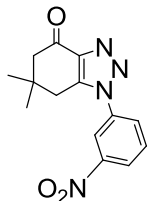


The reaction was also tried with aryl azides bearing electron donating groups such as 4-methylphenyl azide and 4-methoxyphenyl azide but the reaction did not proceed even after 12 h. This different reactivity toward aryl azides with electron donating groups can be explained on the basis of mechanism involved in cycloaddition reaction. 1,3-Cycloaddition takes place by overlapping of frontier molecular orbitals of the 1,3-dipole and the dipolarophile, such orbital overlap may be HOMO controlled dipole or HOMO-LUMO controlled dipole or LUMO controlled dipole. Since in present case reaction does not take place when 1,3-dipole *i.e.* aryl azide bears an electron releasing groups this indicates that reaction take place by LUMO controlled dipole mechanism in which LUMO of 1,3-dipole overlap with HOMO of dipolarophile. The presence of electron releasing functional group on aryl azide (1,3-dipole)

raises the energy of LUMO thus increasing HOMO – LUMO energy gap which make the reaction difficult to proceed even after 12 h.

Recently, Bazgir et. al.²⁰ also reported the synthesis of four fused 1,2,3-triazoles by cycloaddition reaction of dimedone/ 2-hydroxynaphthalene-1,4-dione with *meta* and *para*- nitrophenylazide using TMG as a catalyst in ethanol at 30 °C. The comparison of our method with this reported procedure is shown in **Table 4**. As it can be seen from Table 4 our method found to be much more efficient in terms of both yield and reaction time.

Table 4. Comparison of our method with method reported in literature by Bazgir *et. al*.

S.No.	Product	Yield (%) ^a	Time ^a	Yield (%) ^b	Time ^b
1.		86	45 min	72	3 h
2.		92	20 min	62	7 h
3.		78	45 min	60	7 h

^aYield and time by our method. ^bYield and time by method reported by Bazgir *et. al*

The recyclability of the catalyst and solvent *i.e.* DBU-PEG system was also examined by using model reaction of **1a** (1.0 mmol) with 4-nitrophenyl azide (1.0 mmol) at 80 °C. After completion of the reaction as indicated by TLC, it was cooled and quenched with water (5 mL). The precipitate formed was collected by filtration at pump. The filtrate was concentrated under reduced pressure and dried under vacuum to recover DBU-PEG for the subsequent use. No significant loss in the yield of **2b** was observed after three cycles as **2b** was obtained in 92%, 90% and 86% yield after first, second and third cycle, respectively. Therefore, this catalytic system acts as an excellent recyclable reaction medium for synthesis of fused 1,2,3-triazoles in good yield.

The purity of the recovered DBU-PEG has been confirmed using TLC analysis, which showed the spot corresponding to DBU only. During the recyclability of DBU-PEG water was removed completely. The effect of water on the reaction was also investigated. The aqueous extract obtained after filtration of **2b** was used as such for the next reaction. The reaction was incomplete even after 8 h and the desired product was separated in 38% yield. Thus, removal of water by concentration is essential to reuse the DBU-PEG for a next reaction.

In summary, we have described an efficient synthesis of biologically important fused 1,2,3-triazoles by DBU catalyzed [3 + 2] cycloaddition of aryl azides with activated cyclic C-H acids such as dimedone, cyclohexane-1,3-dione, 5-methylcyclohexane-1,3-dione and 2-hydroxynaphthalene-1,4-dione in PEG-400. All products were obtained in good yields. Metal free experimental procedure, easy available starting materials, short reaction time, recyclability of both catalyst and solvent are major advantages of the present procedure.

Supplementary Material

Spectral data and copies of ¹H NMR and ¹³C NMR spectra are available on the Journal's website.

Acknowledgements:

G.K. thanks the Council of Scientific and Industrial Research, New Delhi, India and H.S. thanks UGC, New Delhi, India for the grant of junior and senior research fellowship. The authors also acknowledge DU-DST for providing HRMS-LC analysis.

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24. *General procedure for the synthesis of fused 1,2,3-triazoles (2a-2o and 3a-3h):* A mixture of aryl azide (1.0 mmol), activated cyclic C-H acid such as dimedone/ cyclohexane-1,3-dione/ 5-methylcyclohexane-1,3-dione/ 2-hydroxynaphthalene-1,4-

dione (1.0 mmol), DBU (10 mol%) and PEG-400 (3 mL) was placed in a 50 mL round-bottomed flask. The reaction contents were stirred magnetically in an oil-bath maintained at 80 °C for appropriate time as mentioned in Table 2 and 3. The progress of the reaction was monitored by TLC (eluent: ethyl acetate : petroleum ether, 50 : 50, v/v). After completion of the reaction, the reaction mixture was allowed to cool to room temperature and was quenched with water (5 mL). The precipitate formed was collected by filtration at the pump and washed with water. Products **2g** and **2l** were further purified by flash column chromatography using ethyl acetate : petroleum ether (80 : 20 v/v) as eluent.

Highlights

- DBU catalysed synthesis of fused triazoles
- High yield of products, short reaction time
- Recyclability of both reaction medium and catalyst

ACCEPTED MANUSCRIPT

Graphical Abstract

DBU catalyzed metal free synthesis of fused 1,2,3-triazoles through [3+2] cycloaddition of aryl azides with activated cyclic C-H acids

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