



Original Article

NaHSO₄-SiO₂ Promoted Solvent-Free Synthesis of Triazolo [1,2-a]indazole-triones

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Abstract:

A new one-pot, efficient three-component condensation of dimedone, urazole and aromatic aldehydes in the presence of silica supported sodium hydrogen sulfate as an effective heterogeneous catalyst for the synthesis of novel Triazolo[1,2-a]indazole-1,3,8-trione derivatives under solvent-free conditions is described.

Keywords: Solvent-free , Dimedone, Urazole, Triazoloindazole,

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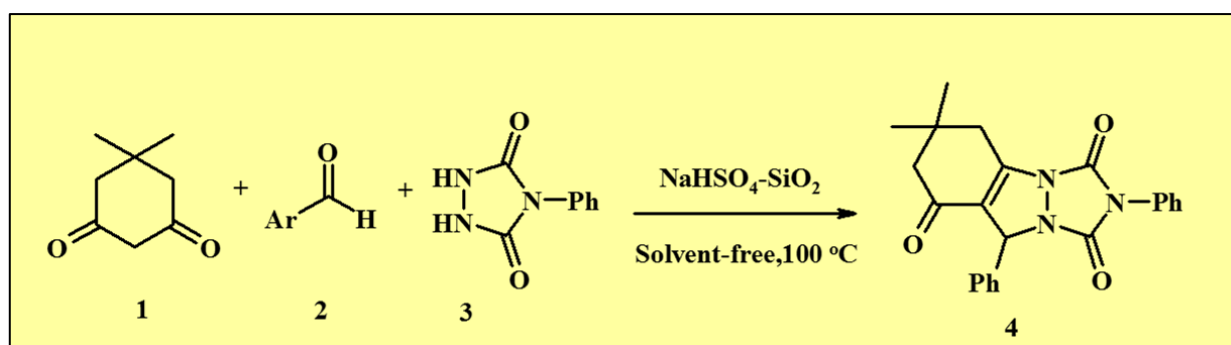
1. Introduction:

Multicomponent reactions (MCRs) enable three or more reactive partners to be combined, either sequentially or simultaneously, in one pot, to give a target library that incorporates diversity simply by varying the constitution of the starting subsets. MCRs are economically and environmentally very advantageous because multi-step syntheses produce considerable amounts of waste, mainly due to complex isolation procedures after each step, often involving expensive, toxic and hazardous solvents [1,2].

Heterocyclic compounds occur widely in Nature and many are essential to life. Nitrogen-containing heterocyclic molecules constitute the largest portion of chemical entities which are part of many natural products, fine chemicals and biologically active pharmaceuticals vital for enhancing the quality of life [3]. Among a large variety of nitrogen-containing heterocyclic compounds, heterocycles containing a urazole (1,2,4-triazolidine-3,5-dione) moiety are of interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activities and clinical applications [4,5].

In recent years, use of heterogeneous catalysts has received considerable interest in various disciplines including organic synthesis. They are advantageous over their homogeneous counterparts due to the prime advantage that, in most cases, the catalyst can be recovered easily and reused. silica supported sodium hydrogen sulfate has been used as an efficient heterogeneous catalyst for many organic transformations because of its low cost, ease of preparation, catalyst recycling, and ease of handling [6–10].

Herein we report a convenient and facile one pot method for the synthesis Triazolo[1,2-a]indazole-triones **4** via Three-Component reaction between dimedon **1**, aromatic aldehydes **2** and 4-phenylurazole **3** under solvent-free conditions in the presence of $\text{NaHSO}_4\text{-SiO}_2$ (Scheme 1).



(Scheme 1)

2. Results and Discussion:

To optimize the amount of catalyst and the reaction temperature, the reaction of 4-chlorobenzaldehyde (1 mmol), dimedone (1 mmol), and urazoles (1 mmol) under thermal solvent-free conditions was selected as a model. The best result was obtained by carrying out the reaction using 0.07 g of NaHSO₄-SiO₂ at 100 °C under solvent-free conditions (Table 1).

Table 1 .Optimization of the amount of SiO₂-NaHSO₄ and the reaction temperature for the preparation of 9-(4-chlorophenyl)-6,7-dihydro-6,6-dimethyl-2-phenyl-[1,2,4]triazolo[1,2- a]indazole-1,3,8(2*H*,5*H*,9*H*)-trione^a

Entry	Catalyst(g)	Reaction conditions	Time (min)	Yield ^b (%)
1	0.04	100 °C	25	71
2	0.05	100 °C	20	76
3	0.07	100 °C	20	84
4	0.1	100 °C	20	80
5	0.07	80 °C	35	74
6	0.07	120 °C	15	73

^a Reaction conditions: Dimedon (1 mmol), 4-phenylurazole (1 mmol), aromatic aldehydes (1 mmol); catalyst: HClO₄-SiO₂ NPs (0.07g); temp: 100 °C; solvent free. ^b Isolated yields.

The efficacy of our protocol was well evaluated using a wide range of aldehydes . As indicated in Table 2, it seemed that there was no remarkable electronic effect from the substituents on aldehyde moiety, since the aryl aldehydes with both electron-donating and electron-withdrawing groups could be applied as efficient candidates for the synthesis of corresponding triazolo[1,2- a]indazolone derivatives in good yields. However, the aliphatic aldehydes reacted slowly as compared to the aryl aldehydes and gave low yields of the products . (Table 2)

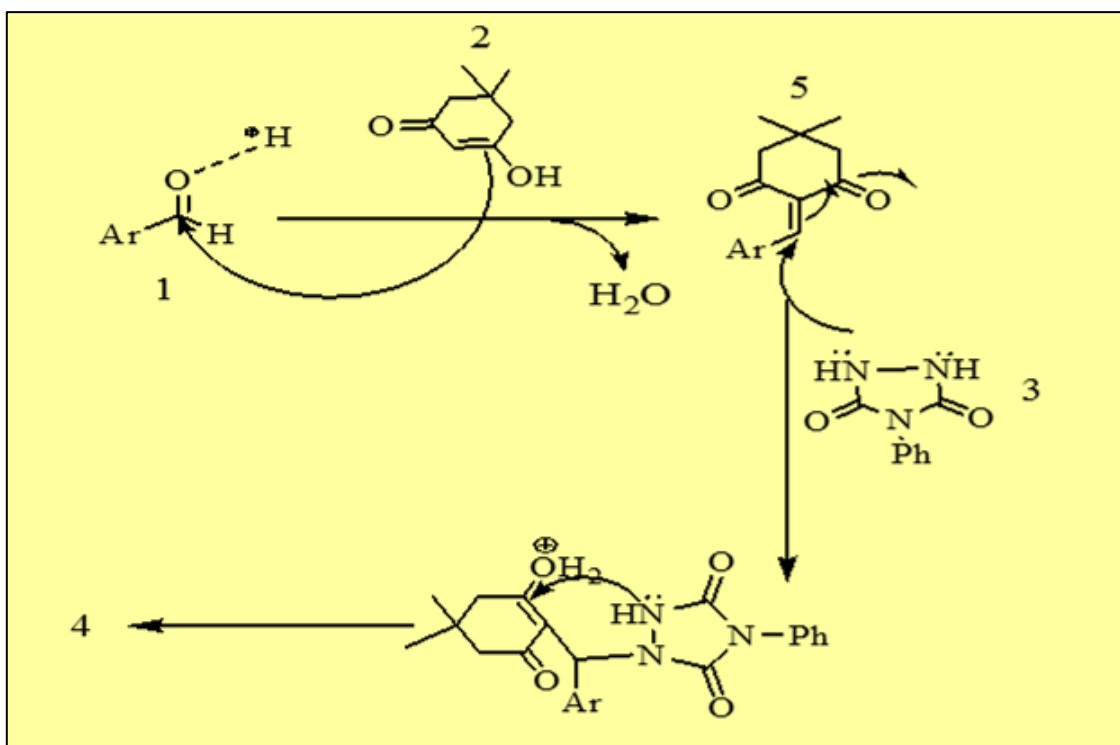
Compounds **4a-h** were known and their structures were deduced by comparison of melting points and spectral data with authentic samples but compounds **4i-j** were new and their structures were deduced by elemental and spectral analysis.[11,13]

Table 2. Three-component reaction of dimedon, 4-phenylurazole and aromatic aldehydes catalyzed by NaHSO₄-SiO₂ under solvent-free conditions^a

Entry	Ar	Time(min)	Yield ^b (%)	M.P. (°C)	mp[lit] (°C)
4a	4-Cl-C ₆ H ₄	20	84	167	166–168 (Bazgir et al., 2007) ¹¹
4b	2-Cl-C ₆ H ₄	20	79	172	175–177 (Bazgir et al., 2007)
4c	C ₆ H ₅	25	78	200	187–189 (Chari et al., 2010) ¹²
4d	4-NO ₂ -C ₆ H ₄	20	81	180	126–128 (Bazgir et al., 2007)
4e	4-Br-C ₆ H ₄	25	80	185	184–186 (Bazgir et al., 2007)
4f	3-Br-C ₆ H ₄	30	81	180	160–162 (Bazgir et al., 2007)
4g	4-Me-C ₆ H ₄	30	79	165	173–175 (Bazgir et al., 2007)
4h	4-MeO-C ₆ H ₄	30	78	175	176–180 (Kidwai et al., 2012) ¹³
4i	2-NO ₂ -C ₆ H ₄	20	80	168	(New product)
4j	2-Me-C ₆ H ₄	25	77	184	(New product)

^a Reaction conditions: Dimedon (1 mmol), 4-phenylurazole (1 mmol), aromatic aldehydes (1 mmol); catalyst: NaHSO₄-SiO₂ (0.07g); temp: 100 °C; solvent free. ^b Isolated yields.

A possible mechanism for the formation of the products is shown in Scheme 2. The reaction occurs via initial formation of heterodiene **5**, by standard Knoevenagel condensation of aldehyde **1** and dimedone **2**. Subsequent Michael-type addition of the urazole **3** to **5** followed by cyclization affords the corresponding product **4** (Scheme 2).



Scheme 2. Suitable mechanism for the formation of triazole[1,2-a]indazoletriones.

Another advantage of this approach could be related to the reusability of the catalyst. We found that the catalyst could be separated from the reaction mixture simply by centrifuge and washing with ethanol and dried at 100 °C. The reusability of NaHSO₄-SiO₂ was checked by the reaction of Dimedon **1**, 4-phenylurazole **2** and aromatic aldehydes **3** under optimized reaction conditions. The results show that the catalyst can be used effectively three times with slight decreasing in catalytic activity, 82%, 76% and 72% (Table4). Therefore, the recyclability of the catalyst makes the process economically and potentially viable for commercial applications.

Table 4. Recyclability of the catalyst^a

No. of cycles ^a	Fresh	Run1	Run2	Run3
Yield ^b (%)	84	82	76	72
Time (min)	20	20	20	20

^a Reaction conditions: Dimedon (1 mmol), 4-phenylurazole (1 mmol), aromatic aldehydes (1 mmol); catalyst: NaHSO₄-SiO₂ (0.07g); temp: 100 °C; solvent free. ^b Isolated yields.

3. Experimental:

3.1. General

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^1H and ^{13}C NMR spectra were recorded on Bruker DRX-500 Avance spectrometer at solution in CDCl_3 using TMS as internal standard. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

3.2. Preparation of $\text{NaHSO}_4\text{-SiO}_2$

Silica supported sodium hydrogen sulfate can be prepared easily from the readily available inexpensive ingredients, $\text{NaHSO}_4\text{-H}_2\text{O}$ and silica gel [14].

3.3. Typical procedure for the synthesis of triazolo[1,2-a] indazole-trione(4a)

In a typical experiment, a mixture of Dimedon (1.0 mmol), 4-phenylurazole (1.0 mmol), aromatic aldehyde (1.0 mmol) and $\text{NaHSO}_4\text{-SiO}_2$ (0.07 g) in solvent-free conditions was heated at 100 °C. The reaction was monitored by thin layer chromatography. The reaction went to completion around 20–30 min. After completion of the reaction, the reaction mixture was cooled at room temperature. The solid residue was dissolved in hot ethanol and centrifuged to separate the catalyst. By recrystallization from ethyl acetate–n-hexane (1:2), pure products were obtained.

6,7-Dihydro-6,6-dimethyl-2-phenyl-9-(4-chloro-phenyl)-[1,2,4]-triazolo[1,2-a]indazole-1,3,8(2H,5H,9H)-trione:

White powder mp >166 °C, yield 86%, IR (KBr) (ν_{max} , cm^{-1}): 1728, 1668, 1088. ^1H NMR (400 MHz, CDCl_3): δ = 1.01 (3H, s, CH_3), 1.12 (3H, s, CH_3), 2.23 (2H, AB system, $^2J_{\text{HH}} = 16.8$ Hz, CH_2), 2.48 (2H, s,

CH₂), 6.21 (1H, s, CH), 7.19-7.51 (9H, m, arom) (ppm). ¹³C NMR (100MHz, CDCl₃): δ = 27.2, 28.3, 35.5, 40.8, 50.6, 63.4, 115.2, 125.6, 128.2, 128.5, 128.8, 129.1, 129.3, 129.8, 135.4, 142.7, 150.9, 162.4, 196.3.

4. Conclusions

In conclusion, we have demonstrated that NaHSO₄-SiO₂ can be used as green and reusable and heterogeneous catalyst for efficient synthesis of triazoloindazoles under solvent-free conditions. Simple reaction, one-pot and work-up procedures make it a useful protocol for the synthesis of these classes of compounds.

5. Acknowledgements

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6. References

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