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Complete List of Authors:	Singh, Praveen; Banaras Hindu University, Chemistry Kumar, Ranjeet; Banaras Hindu University, Chemistry Yadav, Brijesh; Banaras Hindu University, Department of Chemistry Khanna, Ranjana; Banaras Hindu university, Department of Chemistry Tewari, Ashish; Banaras Hindu University, Department of Chemistry

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ARTICLE TYPE

CCSO nano catalyzed solid phase synthesis of 3-oxo-5,6-disubstituted-2,3-dihydropyridazine-4-carbonitrile

Praveen Singh, Ranjeet Kumar, Brijesh Kumar Yadav, Ranjana S. Khanna, Ashish Kumar Tewari*

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Co-doped $Ce_{0.94}Ca_{0.05}Sr_{0.01}O_{1.94}$ (CCSO) nano particle has been successfully synthesized by auto-combustion method and were characterized by XRD, TEM and AFM analysis. The catalytic activity of nano-catalyst is evaluated by the synthesis of substituted pyridazines from substituted benzil and cyano acetylhydrazide which have great biological and pharmaceutical interest. Thus, a highly economically efficient one-pot solvent free synthesis of pyridazine was developed, which is promoted by CCSO nano catalyst. The uniqueness of reaction is very short time (2-4 min) and high yields (90-95%). The method offers highly convergent, inexpensive, and functionality-tolerable procedure for rapid access to important pyridazine compounds in good yields.

1. Introduction

The nitrogen containing six membered heterocyclic compounds especially pyridazines have attracted more attention during recent years due to their novel biological and pharmacological activities.[1] Due to such biological activity, pyridazine derivatives have become the synthetic targets of many organic and medicinal chemistry groups, and new methods for constructing the pyridazine nucleus come out regularly in the literature.

The synthesis of pyridazine frameworks has been achieved primarily by the addition of hydrazine or its derivative to an appropriate 1,4-diketones and 1,4-ketoacids[2-4] in presence of sodium and ethanol solution. Other pyridazines like amino pyridazines have been prepared from poly-functionalized nitriles, especially via the Jaap-Klingemaan reaction.[5-9] The literature also showed the preparation of pyridazines and pyridazinone involving active methylene species, benzil and hydrazine. However, the methods employed harsh bases[10-12] or acids[13] in presence of hazardous solvents; also it requires large duration to complete. Recently, potassium hydroxide impregnated alumina was used for the synthesis of substituted pyridazine from 1,2-dicarbonyls, and hydrazine hydrate in microwave (MW) irradiation.[14] Therefore, there is a need for developing a milder and safer solvent-free procedure for the synthesis of substituted pyridazines especially because of the rise in demand for environmentally benign organic synthesis. To address the challenge of green synthesis, multi-component reactions (MCRs) provide a solution since they are more efficient, cost effective, and less wasteful than traditional methods.

Consequently, we embarked on establishing a new, one-pot procedure, which would be applicable for such aromatic substrates. Herein, we report a simple, efficient and practical one-pot pyridazine synthesis by using nano catalyst $Ce_{0.94}Ca_{0.05}Sr_{0.01}O_{1.94}$ (CCSO), substituted benzil and cyanoacetyl hydrazide, at 110 ºC for 2-4 min.

*Department of Chemistry, Faculty of Science, Banaras Hindu University, Varanasi 221 005, E-mail: tashish2002@yahoo.com, Corresponding author. Tel.: +919935343986; fax: +915422368127;

Electronic supplementary information (ESI) available: Mass, ^{1}H and ^{13}CNMRspectra, synthesis and characterization of 2,4,5-trisubstituted imidazole compound.

The reaction was preceded with a number of 1,2-diketones and use of nano catalyst CCSO was quite enough for catalyze the reaction (Scheme 1). The simple workup procedures make this protocol economically attractive. In this condition, there was no need of column chromatography for purification. For work up process, small amount of ethanol was added for dissolving the product and filtered. Nanocatalyst CCSO is recyclized by drying the residue. Precipitation of dissolved product was occurred by addition of water in filtrate. The precipitate was filtered and washed with excess of water and got 100% pure product. The uniqueness of reaction is very less time (2-4 min) and reusability of catalyst.

2. Results and discussion

Preparation and characterization of CCSO nano particle

We synthesized $Ce_{0.94}Ca_{0.05}Sr_{0.01}O_{1.94}$ (CCSO) nano particle as earlier reported method.[15] Starting chemicals used for the synthesis were ceric ammonium nitrate $(NH_4)_2[Ce(NO_3)_6]$, calcium carbonate, strontium nitrate, and citric acid for the synthesis of powders. Aqueous solutions of metal nitrates were mixed with an aqueous solution of citric acid maintaining a constant citrate to nitrate ratio of 0.3.[16] The mixed solution was evaporated with continuous stirring at 200±5 °C until it gelled and finally burnt. Within a few seconds, the combustion reaction completed giving yellow porous ash filling the container. The ash was calcined at 600 °C in air for 4 h.

Sample characterization

Crystal structure of calcined powder was determined using a Rigaku high-resolution powder X-ray diffractometer employing Cu $K\alpha_1$ radiation and Ni filter. Data were collected in the Bragg angle range of $20° \leq 2\theta \leq 80°$. The crystallite size, D of the calcined powder, was determined using Scherrer's formula:

$$D = 0.9\lambda / \beta\cos\theta$$

Where β is the full width at half maxima excluding instrumental broadening, λ is the wave length of X-ray radiation, and θ is the Bragg angle. β is taken for the strongest Bragg's peak corresponding to (111) reflection for all the samples. Lattice parameters were calculated using "Unit Cell" software.[17] Figure1 shows X-ray diffraction patterns of the calcined powder for the system $Ce_{0.94}Ca_{0.05}Sr_{0.01}O_{1.94}$. Characteristic lines of constituent oxides are not observed in the diffraction patterns. All the samples

are single phase having cubic fluorite structure. X-ray diffraction (XRD) patterns of the calcined powders showed a slight shift in 2θ values from the corresponding 2θ values of undoped ceria. Diffraction patterns were indexed on the basis of fluorite structure similar to CeO_2 using JCPDS file no. 43-1002. Lattice parameter of nano catalyst is given in Table 1.

Table 1. Crystallite size, lattice parameter and percent theoretical density of compositions in the system $Ce_{0.94}Ca_{0.05}Sr_{0.01}O_{1.94}$

Compositions	**$Ce_{0.94}Ca_{0.05}Sr_{0.01}O_{1.94}$**
Crystallite size of sintered powder (nm)	47
Lattice Parameter (Å)	5.4174±0.0002
Experimental density (g/cc)	6.69±0.02
Percent of Theoretical density	98.3

Crystallite size, D of the calcined powder calculated from X-ray line broadening using Scherrer's formula, is in the range 30±10 nm.

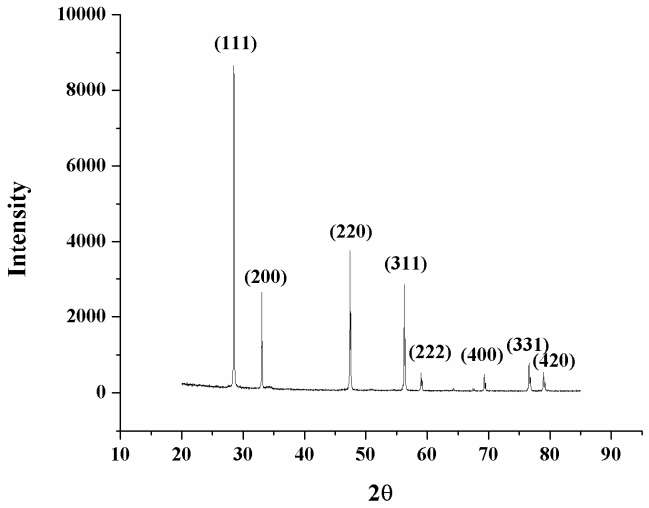
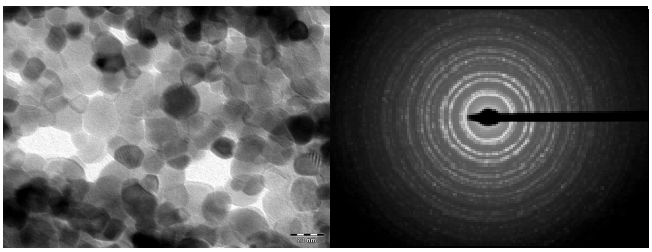


Figure 1. Powder X-ray diffraction patterns of CCSO nanoparticle calcined at 600 °C.

TEM and AFM images (Figure 2 and 3) of the CCSO nanoparticles show the spherical shape, without any aggregation. The average particle size was 30±10 nm, which is consistent with the crystallite size of 30±10 nm calculated from the XRD patterns. The SAED ring patterns in Figure 2 are identified as (111), (200), (220) and (311) planes of a CCSO cubic phase (CaF_2structure).



(a) (b)

Figure 2. TEM images of CCSO nanoparticles synthesized by the two step solvothermal reaction at 600°C. (a): Images of CeO_2 nanoparticles spread on a holey carbon grid; (b): SAED patterns;

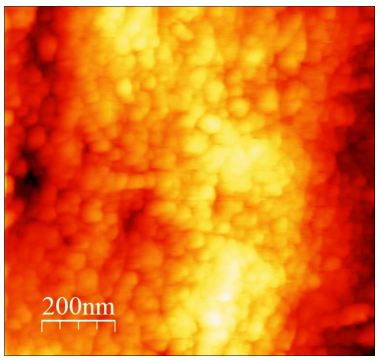


Figure 3. Two dimensional AFM image of CCSO nano particle.

Initially, the pyridazine synthesis was optimized by heating a mixture of benzil and cyanoacetylhydrazide in presence of NaOEt base and MeOH solvent in an oil bath at 70ºC for nine hours which afforded the product in 25% yield. The same reaction when heated in presence of NaOMe base and MeOH solvent at 70 ºC for eight hours gave product in 30% yield. By varying the base in different solvent and heating time, optimization was done in K_2CO_3 base and ethanol solvent at 80ºC which resulted 52% of the product (Table 1). The lower percentage yield of pyridazine is due to incomplete cyclization of cyanoacetohydrazide and benzil. It was observed in TLC. Due to poor yield in base catalyzed reaction, CCSO nanocatalyzed reaction was carried out in EtOH at 80ºC, yield 78% product in 2 hour. Again, optimization was done with CCSO nanocatalyst in MeOH solvent which yielded 82% of the product in 1.5 hour. By exciting the results, CCSO was used in solvent free condition at 105 ºC which resulted 94% of the product in 2 minute. The quantitative analysis of the nanocatalyst was also performed and it was found that the yield of the product increased with increasing amount of catalyst from 10-20 mg respectively for 2 mmol of the reactant. This could be mainly due to the availability of a large number of active sites on the surface of the catalyst, which increases with the amount of the catalyst (Table 2, entries 4–7).

Further scope of the reaction for the synthesis of 3-oxo-5,6-disubstituted-2,3-dihydropyridazine-4-carbonitrile was investigated using CCSO nano catalyst in solvent free condition. Substituted benzil (2 mmol) having electron donating or withdrawing groups led to the formation of products on reaction with cyanoacetohydrazide (2 mmol) at 110 °C and the reactions preceded smoothly in 2-4 minute with yields in the range of 90-95%. Moreover, Nanocat CCSO can be recycled and reused several times without any significant loss of the catalytic activity. Cyanoacetohydrazide was synthesized by mixing of cyanoethylacetate and hydrazine hydrate at 0°C. (**Scheme 1**)

Scheme1. Synthesis of 3-oxo-5,6-disubstituted-2,3-dihydropyridazine-4-carbonitrile compound.

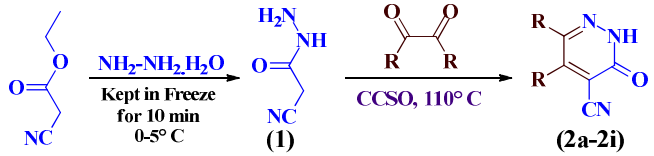
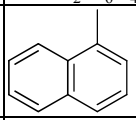


Table 2. Condensation of benzil and 2-cyanoacetohydrazide in the presence of different solvent and catalyst.

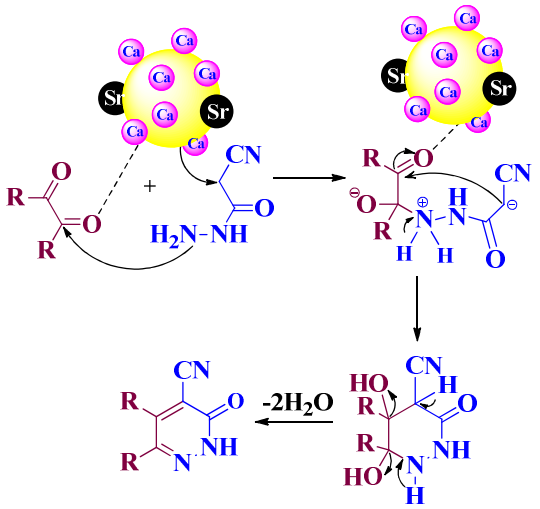
S. No.	Catalyst	Solvent	Temp. (^{0}C)	Time (Hour)	Yield
1	NaOEt	MeOH	70	9	25
2	NaOMe	MeOH	70	8	30
3	t-BuOK	MeOH	70	8.5	32
4	Na	MeOH	70	4	35
5	NaOH	MeOH	70	5	33
6	KOH	MeOH	70	5	31
7	K_2CO_3	MeOH	70	7	27
8	NaOEt	EtOH	80	9.5	32
9	NaOMe	EtOH	80	8	34
10	t-BuOK	EtOH	80	6.5	42
11	Na	EtOH	80	5	40
12	NaOH	EtOH	80	6	47
13	KOH	EtOH	80	7.5	48
14	K_2CO_3	EtOH	80	8.5	52
15	CCSO	EtOH	80	2	78
16	CCSO	MeOH	70	1.5	82
17	CCSO	Solvent free	105	2 min.	94

Consequently, we embarked on establishing a new, one-pot procedure, which would be applicable for such aromatic substrates. Herein, we report a simple, efficient and practical one-pot pyridazine synthesis using inexpensive and readily available reagents. We examined the reaction conditions to a wide range of ortho-, meta- and para- substituted benzils undergo condensation with cyanoacetylhydrazide to promote synthesis of substituted pyridazine (2a-2i) in good yields (Table 3).

Table 3. CCSO catalyzed solvent-free synthesis of substituted pyridazines at 110^{0}C.

S. No.	R	Time (min.)	Yield	M.P. (^{0}C)
2a	Ph	2	94	270-272
2b[14]	Me	2	94	210-212
2c	2-Cl-C_6H_4	3	95	263-265
2d	4-Cl-C_6H_4	4	93	268-270
2e	4-Me-C_6H_4	2	92	287-289
2f	3-NO_2-C_6H_4	2.5	90	302-305
2g		3	95	165-170
2h	4-OMe-C_6H_4	2.5	93	235-236
2i[19]	4-NO_2-C_6H_4	3	92	302-305

A mixture of the cyanoacetylhydrazide 1 (20 mmol)[20], Substituted benzil 2 (20 mmol) and CCSO nano catalyst was added in 100 ml round bottom flask. The reaction mixture was heated at 110 ^{0}C for 2-3 minute. The completion of reaction was monitored through TLC. Since no side reaction occurs and the product was almost pure. The product was dissolved in polar solvent like ethanol by heating and filtered. Ice cold water was added to the filtrate and acidified with HCl. The residue was washed with water, dried and recrystallized from ethyl acetate to get pure substituted pyridazine (2a-2i) without performing any chromatographic procedures and also marked by separation of solid pyridazine product. All the synthesized 3-oxo-5,6-disubstituted-2,3-dihydropyridazine-4-carbonitrile have been characterized on the basis of elemental analysis and spectral studies (Table 2) and the mechanism of CCSO catlysed substituted pyridazine derivative is provided in scheme 2.



Scheme 2. Proposed reaction mechanism.

3. Experimental

3.1 Characterization and methods

All reagents were commercial and purchased from Merck, Aldrich and were used as received. All the reactions were monitored by manually prepared thin layer chromatography over **silica Gel G TLC** plates. The melting points were recorded on electrically heated instrument and are uncorrected. All ^{1}H and ^{13}CNMR spectra were recorded on **JEOLAL300 FT-NMR** spectrometer using tetramethylsilane as the internal reference and chemical shift values are expressed in δ ppm units. Mass spectra of compounds were taken with **JEOL SX 102/Da-600** mass spectrometer. Analysis was performed on Exter Analytical Inc. **"Model CE-440 CHN analyzer"** instrument.

3.2 2-cyanoacetohydrazide synthesis

Ethyl 2-cyanoacetate (226 mg, 2 mmol) and hydrazine hydrate (100 mg, 2 mmol) were mixed in a beaker and added 1 ml ethanol. The resultant mixture was kept in freezer for 10 minute. Then, white crystalline 2-cyanoacetohydrazide was formed. The solid product was filtered and washed with cold ethanol.

M.P.104-105°C; Yield: 0.17g (86%); FAB MS: m/z 100 (M+1); Elemental analysis for $C_3H_5N_3O$: Calcd: C, 36.36; H, 5.09; N, 42.41%; Found: C, 36.31; H, 5.06; N, 42.39%.

3.3 Procedure for the preparation of 3-oxo-5,6-disubstituted-2,3-dihydropyridazine-4-carbonitrile:

A mixture of the cyanoacetylhydrazide (20 mmol), substituted benzil (20 mmol) and CCSO nano catalyst (20 mg) was added in 100 ml round bottom flask. The reaction mixture was heated at 110 ^{0}C for 2-4 minute. Firstly, the reaction mixture melts and become solid. The completion of reaction monitored through TLC. The solid product was dissolved in minimum amount of ethanol (5 ml) through heating and filtered. The residue was filtered and dried. In filtrate, ice cold water was added for precipitation. The precipitate was filtered and washed with excess of water and got 100% pure product. The product was recrystallized from ethyl acetate (5 ml) to yield pure product.

3-oxo-5,6-diphenyl-2,3-dihydropyridazine-4-carbonitrile (2a): M.P.270-272°C; Yield: 5.14g (94%); ^{1}H NMR (300MHz, $CDCl_3$): δ 7.08-7.45 (m, 10H, Ar-H), 11.62 (s, 1H, -NH); ^{13}C NMR (75MHz, $CDCl_3$): δ 113.4, 113.9, 127.9, 128.4, 128.5, 128.7, 129.1, 129.9, 133.3, 134.7, 145.9, 151.8, 157.5; FAB MS: m/z 274 (M+1);

Elemental analysis for $C_{17}H_{11}N_3O$: Calcd: C, 74.71; H, 4.06; N, 15.38%; Found: C, 74.59; H, 4.01; N, 15.27%.

5,6-dimethyl-3-oxo-2,3-dihydropyridazine-4-carbonitrile (2b): M.P. 209–211°C; Yield: 3.07g (94 %); ^{1}H NMR (300MHz, $Si(CH_3)_4$, $CDCl_3$): δ 2.34 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 11.28 (s, 1H, NH); ; FAB MS: m/z 150 (M+1); Elemental analysis for $C_7H_7N_3O$: Calcd: C, 56.37; H, 4.73; N, 28.17%; Found: C, 56.21; H, 4.68; N, 28.32%.

5,6-bis(2-chlorophenyl)-3-oxo-2,3-dihydropyridazine-4-carbonitrile (2c): M.P.263-265°C; Yield: 6.5g (95%);^{1}H NMR (300MHz, $CDCl_3$): δ 7.04-7.41 (m, 6H, Ar-H), 7.61-7.87 (d, 1H, Ar-H), 7.90-7.96 (d, 1H, Ar-H); ^{13}C NMR (75MHz, $CDCl_3$): δ 104.1, 112.3, 126.4, 126.8, 127.6, 128.1, 128.3, 129.5, 129.7, 134.0, 134.1, 137.5, 161.5, 164.6; FAB MS: m/z 342 (M+1); Elemental analysis for $C_{17}H_9Cl_2N_3O$: Calcd: C, 59.67; H, 2.65; N, 12.28%; Found: C, 59.60; H, 2.57; N, 12.24%.

5,6-bis(4-chlorophenyl)-3-oxo-2,3-dihydropyridazine-4-carbonitrile (2d): M.P. 268-270°C; Yield: 6.36g (93%); ^{1}H NMR (300MHz, $CDCl_3$): δ 7.30-7.45 (m, 6H, Ar-H), 7.87-7.89 (d, 2H, Ar-H), 14.42 (s, 1H, -NH); ^{13}C NMR (75MHz, $CDCl_3$): δ 126.2, 130.5, 130.6, 131.2, 133.1, 167.2; FAB MS: m/z 342 (M+1); Elemental analysis for $C_{17}H_9Cl_2N_3O$: Calcd: C, 59.67; H, 2.65; N, 12.28%; Found: C, 59.61; H, 2.59; N, 12.20%.

3-oxo-5,6-di-p-tolyl-2,3-dihydropyridazine-4-carbonitrile (2e): M.P.287-289°C; Yield: 5.54g (92%); ^{1}H NMR (300MHz, $CDCl_3$): δ 3.88 (s, 6H, 2 × CH_3), 7.12-7.36 (m, 6H, Ar-H), 7.51-7.65 (d, 1H, Ar-H), 7.73-7.98 (d, 1H, Ar-H), 12.37 (s, 1H, -NH); ^{13}C NMR (75MHz, $CDCl_3$): δ 20.3, 127.1, 127.3, 127.9, 128.1, 128.5, 128.8, 129.3, 130.1, 132.2, 132.8, 136.9, 142.9, 165.6, 167.5; FAB MS: m/z 302 (M+1); Elemental analysis for $C_{19}H_{15}N_3O$: Calcd: C, 75.73; H, 5.02; N, 13.94%; Found: C, 75.68; H, 4.99; N, 13.89%.

5,6-bis(3-nitrophenyl)-3-oxo-2,3-dihydropyridazine-4-carbonitrile (2f): M.P.302-305°C; Yield: 6.54g (90%); ^{1}H NMR (300MHz, DMSO): δ 7.07-8.73 (m, 8H, Ar-H), 14.41 (s, 1H, NH); ^{13}C NMR (75MHz, DMSO): δ 123.7, 127.3, 130.5, 135.4, 147.9, 166.0; FAB MS: m/z 364 (M+1); Elemental analysis for $C_{17}H_9N_5O_5$: Calcd: C, 56.20; H, 2.50; N, 19.28%; Found: C, 56.14; H, 2.45; N, 19.23%.

5,6-di(naphthalen-1-yl)-3-oxo-2,3-dihydropyridazine-4-carbonitrile (2g): M.P.165-170°C; Yield: 7.09g (95%); ^{1}H NMR (300MHz, $CDCl_3$ + DMSO): δ 7.35-7.61 (m, 6H, Ar-H), 7.86-7.89 (d, 2H, Ar-H), 7.99-8.02 (d, 2H, Ar-H), 8.24-8.26 (d, 2H, Ar-H), 9.00-9.03 (d, 2H, Ar-H), 12.18 (s, 1H, NH); ^{13}C NMR (75MHz, $CDCl_3$ + few drops of DMSO): δ 124.3, 125.8, 125.9, 127.2, 127.5, 128.2, 130.2, 131.2, 132.8, 133.6, 165.0, 169.5; FAB MS: m/z 374 (M+1); Elemental analysis for $C_{25}H_{15}N_3O$: Calcd: C, 80.41; H, 4.05; N, 11.25%; Found: C, 80.37; H, 4.01; N, 11.19%.

5,6-bis(4-methoxyphenyl)-3-oxo-2,3-dihydropyridazine-4-carbonitrile (2h): M.P. 235-236°C, Yield: 6.45 g (93 %),^{1}H NMR(300MHz, $Si(CH_3)_4$, $CDCl_3$): δ 4.04 (s, 3H, OCH3), 7.19-8.47 (m, 8H, Ar-H),14.19(s,1H,-NH); ^{13}C NMR (75MHz, $CDCl_3$): δ 112.4, 125.9, 134.4, 164.9; FAB MS: m/z 334 (M+1); Elemental analysis for $C_{19}H_{15}N_3O_3$: Calcd: C, 68.46; H, 4.54; N, 12.61%; Found: C, 68.42; H, 4.56; N, 12.59%.

5,6-bis(4-nitrophenyl)-3-oxo-2,3-dihydropyridazine-4-carbonitrile (2i): M.P.302-305°C; Yield: 6.93g (92 %); ^{1}H NMR (300MHz, $Si(CH_3)_4$, $CDCl_3$): δ 7.65-8.70 (m, 8H, Ar-H); ^{13}CNMR (75MHz, $CDCl_3$,): δ122.75, 125.39, 126.39, 129.51, 130.08, 130.48, 131.60, 132.13, 132.94, 143.74, 147.71, 166.12, 166.77; FAB MS: m/z 364 (M+1); Elemental analysis for $C_{17}H_9N_5O_5$: Calcd: C, 56.20; H, 2.50; N, 19.28%; Found: C, 56.14; H, 2.45; N, 19.23%.

Conclusion

Conclusion part of the manuscript clearly says that if the reaction can be carried out under ecofriendly condition, why to divert towards hazardous organic chemicals. Importance and need of substituted pyridazine nucleus in pharmaceutics as well as a catalyst enforced to synthesize in bulk, thus the aforesaid methodology can be economically and environmentally used in large scale production of 3-oxo-5,6-disubstituted-2,3-dihydropyridazine-4-carbonitrile from aromatic, as well as aliphatic 1,2-diketone in solvent free condition. We have developed a rapid, simple, and highly effective one-pot synthesis of substituted pyridazine. The reaction proceeds via CCSO nano catalyst with a wide variety of benzil and cyanoacetohydrazide. The simple workup procedures make this protocol economically attractive and also reduce the operating time and the amount of waste produced.

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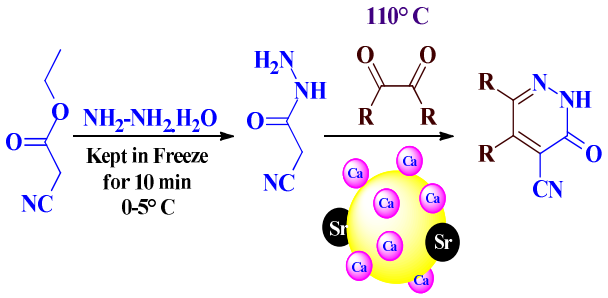
Graphical abstract



CCSO nano particle has been successfully catalyzed the synthesis of substituted pyridazines from substituted benzil and cyanoacetylhydrazide.