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Zinc oxide-Catalyzed Solvent-Free Mechanochemical Route for C-S Bond Construction: A Sustainable Process

P. Md. Khaja Mohinuddin[a], N. C. Gangi Reddy[a]*

Abstract: Zinc oxide-catalyzed solvent-free mechanochemical route has been developed for the rapid construction of C-S bond using a variety of thiols and phenacyl/benzyl/alkyl bromides via a nucleophilic substitution (S_N2 mechanism). Notable advantages of this method include broad substrate scope, cleaner reaction profile, safe, scalable, high yields at ambient conditions and reuse of catalyst. Further, the prepared synthetic precursors are valuable building blocks in the synthesis of various biologically active molecules.

Introduction

Construction of carbon–heteroatom bond has strategic importance in organic synthesis. Among them, the carbon-sulfur (C–S) bond formations[1] have attracted much attention as the C-S bond is indispensable in many bioactive natural products and synthetic drugs, e.g., 1-6 (Fig.1).[2] Furthermore, the top 10 selling drugs in the year 2012 were organosulfur compounds.[3] Among the plethora of organosulfur compounds, organosulfides/thioethers are widely present in nature, various biological systems, foods, materials and pharmaceuticals.[4] Moreover, organosulfides in different oxidative states, e.g., sulfone and sulfoxide, demonstrate divergent functions and potencies as well.[4f] Thus, these functionalities are considered as very attractive building blocks in the syntheses of valuable chemical entities of biological importance.[5] Because of their broad-based utility, enormous research has been conducted and many efficient methods are proposed for the synthesis of various organosulfide/thioether derivatives.[6-14] In spite of this development, there are still some shortcomings such as narrow substrate scope, use of expensive techniques, hazardous chemicals and solvents, low yields of products, time consuming, formation of unwanted side products and complicated work-up procedures. Hence, the development of green and sustainable synthetic methodologies for the construction of C-S bond is still in demand.

Avoiding the use of toxic solvents in organic synthesis is an important step towards developing environmentally benign chemical technologies. Mechanochemical technique has been recognized as an important green technique in synthetic organic chemistry, because it has several advantages such as elimination of large volumes of harmful organic solvent, easy to handle, comparatively cheaper to operate, efficient reaction rate, better selectivity and simple work-up procedure and provides routes to compounds that are not obtained through common synthetic methods.[15] Further, it is carried out in the absence of, or with minimal use of solvents.[16] Aforesaid factors are very essential in industries for the development of sustainable chemical process.[17] To the best our knowledge, there are no reports on mechanochemical synthesis of organosulfide derivatives under solvent free conditions using ZnO. Zinc oxide is a heterogeneous, non-toxic, non corrosive, cheap, moisture stable, environmentally benign catalyst[18] which is also employed in many organic transformations such as Beckmann rearrangements,[19] Biginelli Reaction,[20] Friedel–Crafts acylation,[21] syntheses of cyclic ureas,[22] dehydration of aldoximes,[23] and oxidation of alcohols.[24]

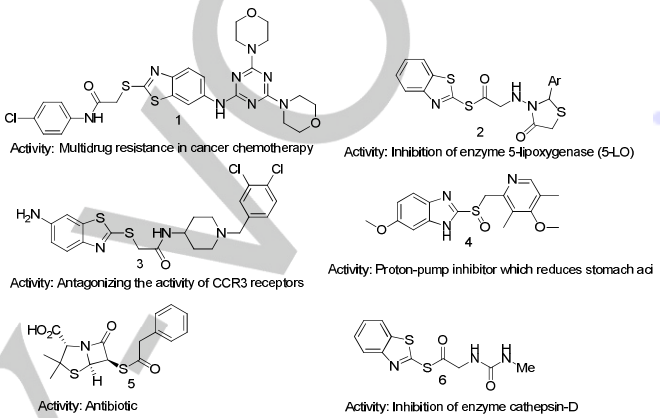
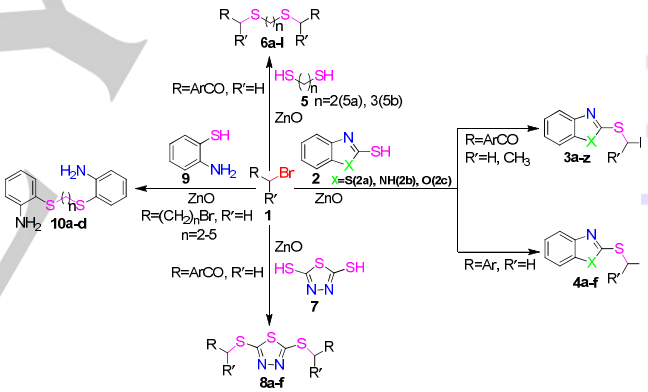


Fig.1 Representative examples of biologically active organosulfur compounds



Scheme: 1 Solvent-free mechanochemical synthesis of diversified organosulfides

In the present communication, a facile mechanochemical route is adopted for the construction of C-S bond, using a variety of thiols and phenacyl/benzyl/alkyl bromides in the presence of ZnO at 25-30℃ for 4-5 minutes under solvent-free conditions via grinding (Scheme 1).

Results and Discussion

Suitable conditions for the synthesis of a library of organosulfide derivatives from various thiols and phenacyl/benzyl/alkyl bromides *via* a nucleophilic substitution (S_N2 mechanism) using solvent-free mechanochemical method (SFMM) are worked out by studying the reaction of phenacyl bromide (**1a**) (10.0 mmol) with 2-mercaptobenzothiazole (**2a**) (10.0 mmol) in presence of K_2CO_3 (5.0% w/w) at 25-30℃ for 20 min. The yield obtained is 35% (entry 1, Table 1). To improve the yield, the same reaction is repeated by employing various catalysts, like Na_2CO_3, Al_2O_3, SiO_2, Fe_2O_3, MgO, CaO, ZnO, TiO_2 and Ag_2O at 25-30℃ and the results are summarized in Table 1. After the examination of various catalysts, it is found that ZnO is the best option to obtain better yield (70%) of

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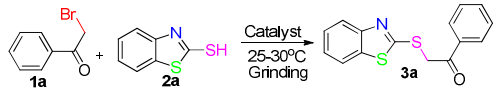
the product (**3a**) (entry 8, Table 1) and other catalysts give low yields of **3a** (entries 1-7, 9 & 10, Table 1). The same reaction is carried out in solvents such as H_2O and ethanol using 5.0% w/w of various catalysts, like K_2CO_3 Na_2CO_3, Al_2O_3, SiO_2, Fe_2O_3, MgO, CaO, ZnO, TiO_2 and Ag_2O at 25-30℃ for 150 min and the obtained results are presented in Table 1. From this study, it is observed that ZnO in ethanol afforded moderate yield (50%) of the product (**3a**)(entry 8, Table 1) and other catalysts provide low yields of product **3a** (entries 1-7, 9 & 10, Table 1). Further, the load of amount of ZnO (5.0%, 10.0%, 15.0% and 20.0% w/w) is also varied for optimization of reaction conditions and the obtained results are presented in Table 2. To our delight, it is found that, loading of 10.0% w/w of ZnO gives the maximum yield of product **3a** in both solvent-free mechanochemical reaction conditions (SFMRC) (98%) and also in the presence of ethanol (75%) (entry 2, Table 2); however, further increasing the amount of ZnO, 15.0 and 20.0% w/w, the product yield remained the same (entries 3 and 4, Table 2). From the above study, it is found that the solvent-free mechanochemical reaction (SFMR) is superior than the reaction in ethanol in giving the utmost yield of product **3a** obtained in a short period of time.

Table 1. Screening of suitable catalyst for the construction of C-S bond.[a]



Entry	Catalyst	Solvent	Product	Solvent		SFMRC	
				Time (min)	Yield[b] (%)	Time (min)	Yield[b] (%)
1	K_2CO_3	H_2O	**3a**	240	15	20	35
		Ethanol		150	30		
2	Na_2CO_3	H_2O	**3a**	240	10	20	30
		Ethanol		150	20		
3	Al_2O_3	H_2O	**3a**	240	5	20	40
		Ethanol		150	25		
4	SiO_2	H_2O	**3a**	240	5	20	30
		Ethanol		150	20		
5	Fe_2O_3	H_2O	**3a**	240	15	20	25
		Ethanol		150	30		
6	MgO	H_2O	**3a**	240	15	20	50
		Ethanol		150	35		
7	CaO	H_2O	**3a**	240	10	20	46
		Ethanol		150	30		
8	ZnO	H_2O	**3a**	240	20	20	70
		Ethanol		150	50		
9	TiO_2	H_2O	**3a**	240	5	20	35
		Ethanol		150	20		
10	Ag_2O	H_2O	**3a**	240	5	20	25
		Ethanol		150	20		
11[c]	**-**	H_2O	**3a**	240	-	20	-
		Ethanol		150	-		

[a]**Reaction conditions:** Phenacyl bromide (1a) (10.0 mmol), 2-mercapto benzothiazole (2a) (10.0 mmol), catalyst (5.0% w/w) at 25-30℃ in the presence of solvents/under solvent-free mechanochemical reaction conditions (SFMRC). [b]Isolated yields. [c]Reaction didn't proceed in the absence of catalyst.

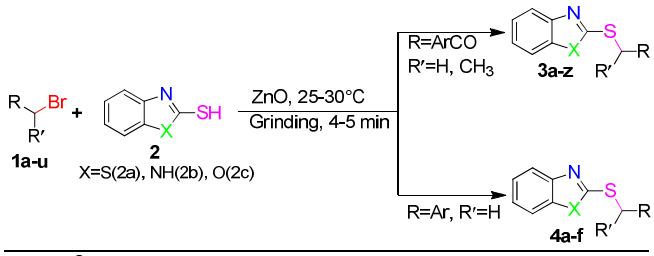
Table 2. Screening of load of catalyst on the course of C-S bond formation.[a]

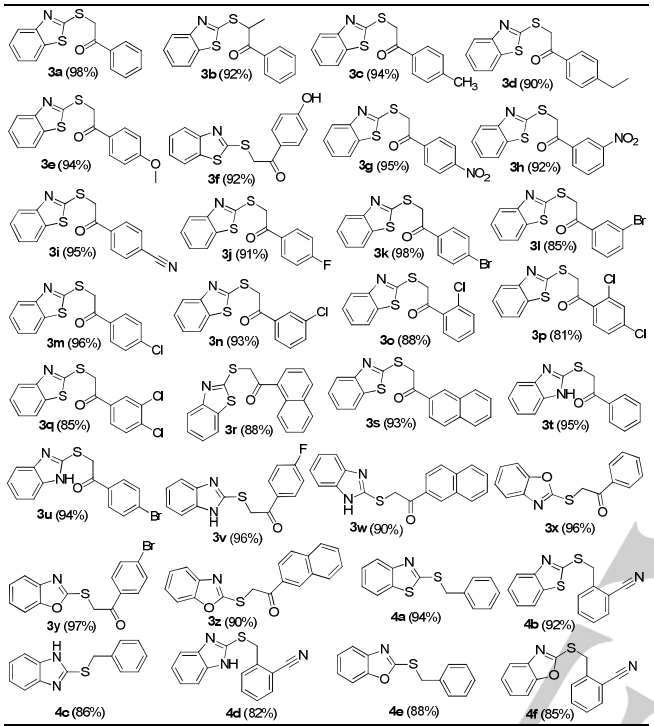
Entry	ZnO (%, w/w)	Solvent	Product	Solvents		SFMRC	
				Time (min)	Yield[b] (%)	Time (min)	Yield[b] (%)
1	5.0	Ethanol	**3a**	150	50	20	70
2	10.0	Ethanol	**3a**	120	75	5	98
3	15.0	Ethanol	**3a**	120	73	5	96
4	20.0	Ethanol	**3a**	120	72	5	96

[a]**Reaction conditions:** Phenacyl bromide (1a) (10.0 mmol), 2-mercapto benzothiazole (2a) (10.0 mmol), catalyst (% w/w) at 25-30℃ in the presence of solvents/under solvent-free mechanochemical reaction conditions (SFMRC). [b]Isolated yields.

With the help of the above optimized reaction conditions, the scope of the present method is studied and the obtained results are presented in Table 3. The parent phenacyl bromide (**1a**) reacts with heterocyclic thiols (**2a**, **2b** and **2c**) to afford the corresponding sulfide derivatives, **3a**, **3t** and **3x** in 98%, 95% and 96% isolated yields respectively. The presence of methyl group at α-carbon of the phenacyl bromide (**1b**) reacts with 2-mercaptobenzothiazole (**2a**) and afforded the product **3b** in 92% yield. Phenacyl bromides (**1c-1f**) with electron-donating groups, such as 4-methyl, 4-ethyl, 4-methoxy and 4-hydroxy groups, showed good reactivity with 2-mercaptobenzothiazole (**2a**) and produce the corresponding thioether derivatives, **3c-3f** in 94-90% yields. Phenacyl bromides (**1g-1j**) bearing strong electron-withdrawing groups such as 4-nitro, 3-nitro, 4-nitrile and 4-fluoro groups react with 2-mercaptobenzothiazole (**2a**) and give the corresponding products, **3g-3j** in excellent isolated yields i.e. 95-91%. From this study, it is observed that the catalyst works efficiently for both electron-donating and electron-withdrawing groups. This may be due to the amphoteric nature of zinc oxide. Phenacyl bromides (**1k and 1m**) with bromo and chloro groups at *para*-position exhibited good reactivity with 2-mercaptobenzothiazole (**2a**) and provided better yields of the products **3k** and **3m** when compared to the bromo and chloro groups present at *meta and ortho* positions (**1l, 1n** and **1o**). 4-bromophenacyl bromide (**1k**) exhibits good reactivity towards heterocyclic thiols (**2b** and **2c**) to afford the corresponding thioethers, **3u** and **3y** in 94% and 97% yields. 4-fluorophenacyl bromide (**1j**) reacts with 2-mercaptobenzimidazole (**2b**) to give the product (**3v**) in 96% yield. It is also found that the presence of dichloro substituents i.e. 2, 4- and 3, 4- dichloro phenacyl bromides (**1p** and **1q**) provide lower yields of products (**3p** and **3q**). The main reason for the decreasing of yields may be due to steric effects. α-bromo acetonaphthones (**1r** and **1s**) also react with heterocyclic thiols (**2a**, **2b** and **2c**) and give the products **3r**, **3s**, **3w** and **3z** in 88-93% yields. Further, it is observed that the benzyl bromide (**1t**) and 2-nitrile benzyl bromide (**1u**) react with heterocyclic thiols (**2a**, **2b** and **2c**) and provide the corresponding products (**4a-4f**) in 94-85% yields. From the above study, it is found that all the functional groups are well tolerated.

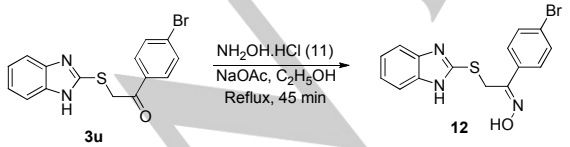
Table 3. Construction of C-S bond using various phenacyl bromides/benzyl bromides and thiols.[a,b]





[a]**Reaction conditions:** Phenacyl bromides/bromo methylbenzene(10.0 mmol), 2-mercaptobenzothiazole/2-mercaptobenzimidazole/2-mercaptobenzoxazole (10.0 mmol), ZnO (10.0% w/w) at 25-30℃ for 4-5 min. [b]Isolated yield.

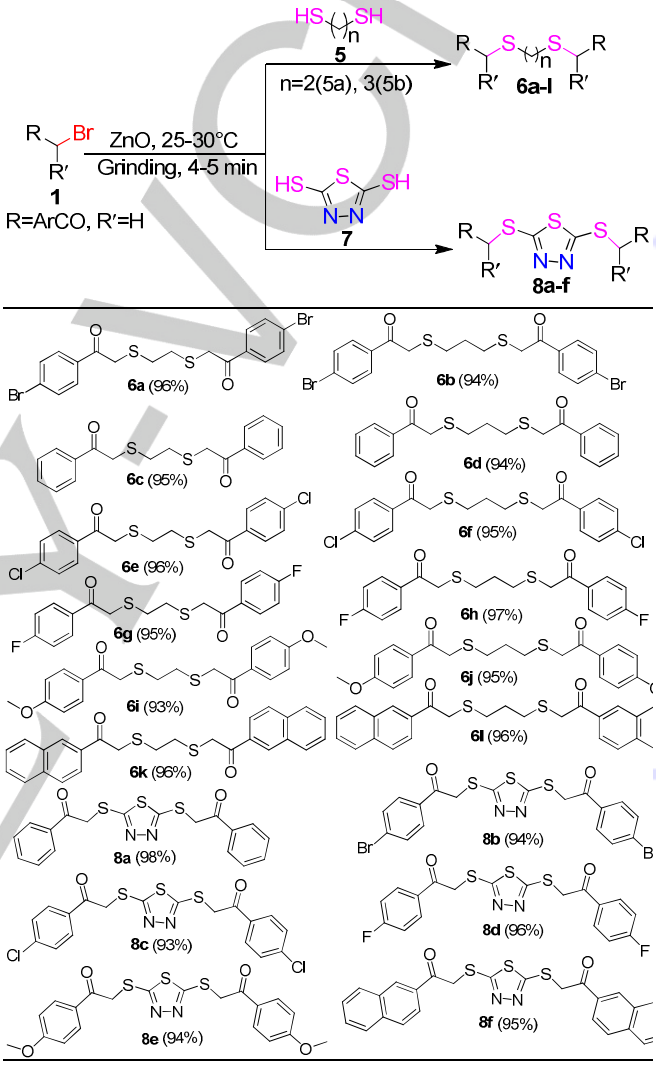
Further, the feasibility of functional group transformations of synthesized compounds (**3a-z**) is also investigated. For this purpose, the reaction has been conducted between 2-(1H-benzo[d]imidazol-2-ylthio)-1-(4-bromophenyl)ethanone (**3u**) (10.0 mmol) and $NH_2OH.HCl$ (**11**) (20.0 mmol) in the presence of NaOAc (15.0 mmol w.r.t. $NH_2OH.HCl$) in ethanol under reflux conditions[25] for 45 min to form the corresponding oxime (**12**), in 98% yield (Scheme. 2). The same reaction is performed under solvent-free mechanochemical reaction conditions (SFMRC) at 25-30℃ for 50 min and found that reaction proceeded with low yield (45%) of product (**12**). Subsequently, 5-6 drops of ethanol is added to the reaction mixture and again ground for another 20 min, the yield of the product (**12**) is increased to 60%.



Scheme 2. Conversion of ketone (**3u**) into oxime derivative (**12**).

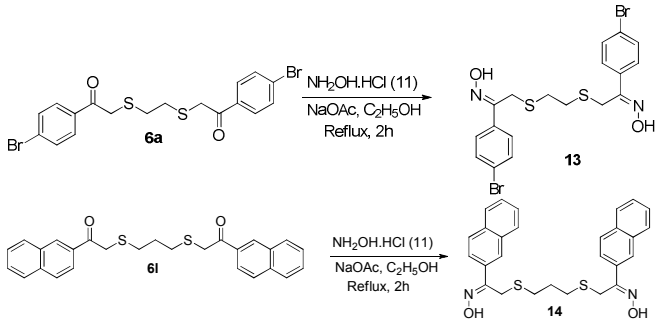
Encouraged by the above results, the substrate scope of dithiols is also examined with various phenacyl bromides. Towards this direction, the reaction mixture of 1, 2- ethanedithiol (**5a**) (5.0 mmol), 4-bromo phenacyl bromide (**1k**) (10.0 mmol) and ZnO (5.0% w/w) under similar conditions results in a 65% yield of product (**6a**). Further, the yield of the product is promoted to 96% by increasing the load of ZnO, 5.0% to 10.0% w/w. The same procedure is applied for various phenacyl bromides and dithiols and the obtained results are presented in Table 4. All the reactions are completed within 4-5 min which affords the desired products **6a-l** and **8a-f**.

Table 4. Formations of C-S bond using various phenacyl bromides and dithiols.[a,b]



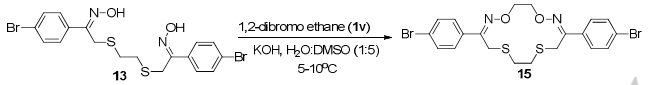
[a]**Reaction conditions:** Phenacyl bromides (10.0 mmol), dithiols (5.0 mmol), ZnO (10.0% w/w) at 25-30℃ for 4-5 min. [b]Isolated yield.

Subsequently, the feasibility of functional group transformations of the synthesized compounds (**6a-l**) is also studied. For this purpose, diketones, **6a** (10.0 mmol) and **6l** (10.0 mmol) are treated with $NH_2OH.HCl$ (**11**) (40.0 mmol) in the presence of NaOAc (30.0 mmol w.r.t.$NH_2OH.HCl$) in ethanol under reflux conditions[25] for 2h to give the corresponding dioximes (**13** & **14**), in 96% and 94% yields, respectively (Scheme.3).The same reactions are carried out under solvent-free mechanochemical reaction conditions (SFMRC) at 25-30℃ for 80 min and found that reactions proceeded with very low yields (30% & 25%) of products (**13** & **14**), respectively. Subsequently, 5-6 drops of ethanol is added to the reaction mixtures and again ground for another 30 min, the yields of the products (**13** & **14**) increased to 45% and 38%, respectively.



Scheme 3. Conversion of diketones (**6a** & **6l**) into dioximes (**13** & **14**).

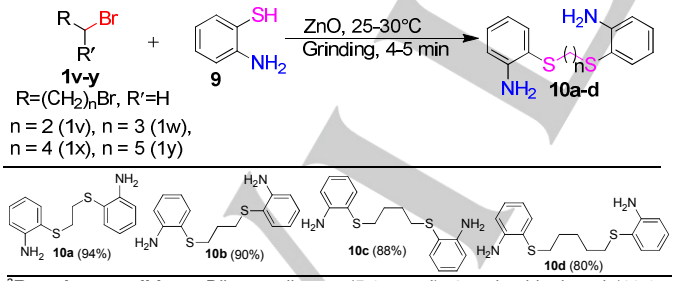
Further, a new class of 14-membered small macrocyclic compound, (2Z,10Z)-3,10-bis(4-bromophenyl)-1,12-dioxa-5,8-dithia-2,11-diazacyclotetradeca-2,10-diene (**15**) is successfully achieved by the reaction of dioxime, **13** (10.0 mmol) and 1,2-dibromo ethane (**1v**) (10.0 mmol) in the presence of KOH (20.0 mmol) in a mixture of H_2O-DMSO (1:5 ratio) at 5-10 ℃ for about 25-35min.[26] The yield of the desired 14-membered macrocyclic molecule (**15**) is 94% (Scheme. 4). The same reaction is executed under mechanochemical conditions at 25-30 ℃ for 40 min and observed that the reaction didn't proceed to give the desired 14-membered macrocyclic molecule (**15**).



Scheme 4. Conversion of dioxime (**13**) into 14-membered macrocycle (**15**).

As a part of the protocol, the substrate scope of the dibromo alkanes is tested with 2-aminothiophenol. For this purpose, initially ground the reaction mixture of 1,2-dibromo ethane (**1v**) (5.0 mmol), 2-aminothiophenol (**9**) (10.0 mmol) and ZnO (10.0% w/w) for 4-5 min at 25-30 ℃, which results in a 60% yield of product (**10a**). Further, the yield of the product is promoted to 94% by increasing the load of ZnO, 10.0% to 20.0% w/w. Different types of dibromo alkanes are examined and the obtained results are summarized in Table 5. All the reactions are completed within 4-5 min which gave the desired products **10a-d**.

Table 5. Construction of C-S bond using various dibromoalkanes and 2-aminothiophenol.[a,b]



[a]**Reaction conditions:** Dibromoalkanes (5.0 mmol), 2-aminothiophenol (10.0 mmol), ZnO (20.0% w/w) at 25-30 ℃ for 4-5min. [b]Isolated yield.

Further, to test the scalability of the procedure, the reaction is conducted between 4-bromo phenacyl bromide (**1k**) and 2-mercaptobenzothiazole (**2a**) in presence of ZnO using mechanochemical technique in different gram scale reactions (1.0, 5.0, 10.0, 15.0, 20.0 and 25.0 grams) which results in 98%, 98%, 97%, 95%, 94% and 94%, yields of product **3k** respectively (Fig.2). From this investigation, it is found that the developed solvent-free mechanochemical synthetic route is a promising greener alternative for the construction of C-S bond in gram-scale production.

The reusability of the catalyst (ZnO) is also tested in the model reaction for the preparation of **3a** using phenacyl bromide (**1a**) and 2-mercaptobenzothiazole (**2a**). After completion of the first cycle, the catalyst is recovered by filtration and washed with ethyl acetate followed by water, dried under vacuum and then reused in the next cycles. The yields obtained for the product **3a** are 98%, 97%, 95%, 93% and 88% for first, second, third, fourth and fifth recycle respectively.

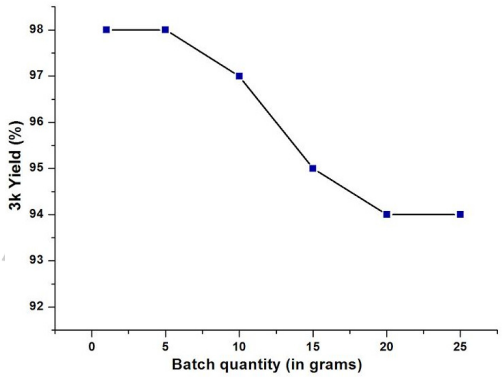
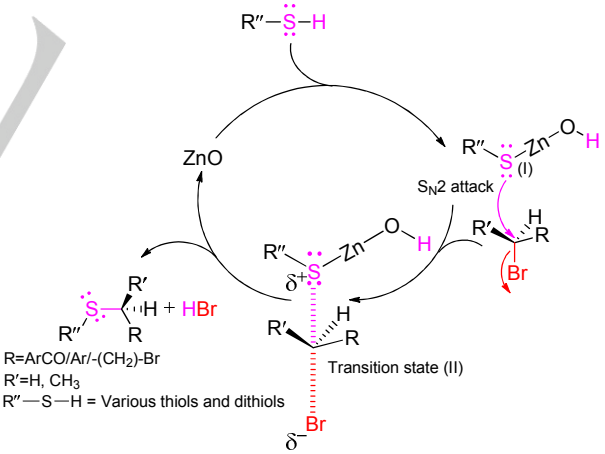


Fig.2. Gram scale synthesis of organosulfides.

A plausible mechanism for the formation of C-S bond in the presence of ZnO as catalyst is depicted in Scheme 5. The mechanism begins with coordination of the thiols to the zinc oxide, followed by a proton transfer from sulphur to oxygen to generate a sulphur-centred nucleophile (I). Subsequently, the S_N2 attack of the nucleophile (I) at the CH_2/CH group of the alkyl bromides leads to the formation of thioether derivatives through a transition state (II).



Scheme 5. Plausible mechanism for the formation of C-S bond in the presence of ZnO.

Conclusions

A simple, robust and solvent-free mechanochemical method has been demonstrated for the construction of C-S bond by the reaction of various thiols (heterocyclic thiols, alkane dithiols and aromatic thiols) with phenacyl/benzyl/alkyl bromides in presence of ZnO via a nucleophilic substitution (S_N2 mechanism). This method has many advantages: easy to perform, wide substrate scope, cleaner reaction profile, rapid, scalable, cost-effective, high yields of products and free from chromatographic purification. The catalyst can be

recovered and reused without significant loss of catalytic activity up to five cycles. Hence, the established synthetic route is an alternative to existing processes for C-S bond formation. Further, the prepared synthetic precursors are suitable for further functional group transformations in the development of new chemical entities of potential pharmacological interest.

Experimental Section

Melting points of various products obtained are determined (uncorrected). ^{1}H NMR and ^{13}C NMR spectra are recorded on a Varian 400 MHz (100 MHz). Chemical shifts are reported in ppm with the internal TMS signal at 0.0 ppm as a standard. The data are reported as follows: chemical shift (ppm) and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, br s = broad singlet), coupling constant(s) in Hz, integration assignment. Mass spectral data are acquired on Exactive Orbitrap mass spectrometer (Thermo Scientific, Waltham, MA, USA) equipped with Thermo Accela 600 quaternary gradient pump and MS source is equipped with electro spray ionization (ESI) probe and it is operated in the positive mode. Thin-layer chromatography is performed on 0.25 mm Merck silica gel plates and visualized with UV light. All chemicals and solvents are purchased from Sigma Aldrich, Acros organics Ltd, Merck and are used as received. Millipore double distilled water is used for the workup process. All phenacyl bromides are prepared as per the reported method in the literature.[27]

General experimental procedure:

General procedure for the synthesis of 2-(benzo[d]thiazol/imidazol/oxazol-2-ylthio)-1-aryl/naphthyl ethanone derivatives and 2-(benzylthio)benzo[d]thiazole/2-(benzylthio)-1H-benzo[d]imidazole/2-(benzylthio)benzo[d] oxazole derivatives (3 & 4):

A mixture of phenacyl bromide (**1a**) (10.0 mmol), 2-mercaptobenzothiazole (**2a**) (10.0 mmol) (**2c**) and ZnO (10.0% w/w) is ground together with a pestle for 4-5 min in a mortar at 25-30^{o}C. At this stage the progress of the reaction is monitored by TLC. After completion of the reaction, the crude mass is washed with water (2x10 mL) twice and extracted with ethyl acetate (2x6 mL) twice. Then the catalyst is separated by filtration under vacuum. The organic layer is washed with water, dried with anhydrous $MgSO_4$ and the solvent is evaporated under reduced pressure. The obtained product (**3a**) is purified by recrystallization using ethanol. The same procedure is applied for the preparation of all other compounds (**3b-z** & **4a-f**). The spectroscopic data of the synthesized compounds (**3a-z** & **4a-f**) are in accordance with their proposed structures.

General procedure for the synthesis of 2,2'-(ethane/(propane -1,2/1,3-diylbis(sulfanediyl))bis(1-aryl/naphthalen-2-ylethanone) derivatives and 2,2'-((1,3,4-thiadiazole-2,5-diyl)bis(sulfanediyl))bis(1-aryl/naphthalen-2-ylethanone) derivatives (6 & 8):

A mixture of 4-bromophenacyl bromide (**1k**) (10.0 mmol) and ethane-1, 2-dithiol (**5a**) (5.0 mmol) and ZnO (10.0% w/w) is ground together with a pestle for 4-5 min in a mortar at 25-30^{o}C. At this stage the progress of the reaction is monitored by TLC. After completion of the reaction, the crude mass is washed with water (2x10 mL) twice and extracted with ethyl acetate (2x6 mL) twice. Then the catalyst is separated by filtration under vacuum. The organic layer is washed with water, dried with anhydrous $MgSO_4$ and the solvent is evaporated under reduced pressure. The obtained product (**6a)** is purified by recrystallization using ethanol. The same procedure is applied for the preparation of all other compounds (**6b-l** & **8a-f)**. The spectra of the synthesized compounds (**6a-l** & **8a-f**) are in accordance with their proposed structures.

General procedure for the synthesis of 2, 2'-(alkyl-diylbis (sulfanediyl))dianiline derivatives (10):

A mixture of 2-aminothiophenol (**9**) (10.0 mmol), 1, 2-dibromoethane (**1v**) (5.0 mmol) and ZnO (20.0% w/w) is thoroughly ground with a pestle in a mortar at 25-30^{o}C for 4-5 min. At this stage the progress of the reaction is monitored by TLC. After completion of the reaction, the crude mass is washed with water (2x10 mL) twice and extracted with ethyl acetate (2x6 mL) twice. Then the catalyst is separated by filtration under vacuum. The organic layer is washed with water, dried with anhydrous $MgSO_4$ and the solvent is evaporated under reduced pressure. The obtained product (**10a**) is purified by recrystallization using ethanol. The same procedure is applied for the preparation of all other compounds (**10b-d**). The spectra of the synthesized compounds (**10a-d**) are in accordance with their proposed structures.

General procedure for the synthesis of 2-((1H-benzo[d]imidazol-2-yl)thio)-1-(4-bromophenyl)ethanone oxime (12)[25]: In a 100-mL two necked round bottom flask, 2-(1H-benzo[d]imidazol-2-ylthio)-1-(4-bromophenyl) ethanone (**3u**) (10.0 mmol) and hydroxyl ammonium chloride ($NH_2OH.HCl$) **(11)** (20.0 mmol) are dissolved in ethanol (20 mL) and then NaOAc (15.0 mmol w.r.t $NH_2OH.HCl$) is added. Then, the reaction mixture is stirred at reflux temperature for 45 min. The progress of the reaction is monitored by TLC. After completion of the reaction, reaction mixture is cooled to RT and then filtered, washed thoroughly with ethanol. The filtrate is collected and the solvent is removed under reduced pressure. To the crude reaction mass, water (25 mL) is added and the product **(12)** is extracted with EtOAc (2x10 mL). Then the organic layer is collected and washed with water (2x25 mL) twice, dried over anhydrous $MgSO_4$ and the solvent is removed under reduced pressure. The crude product (**12)** is recrystallized from the ethanol (5 mL) and n-hexane (15 mL) mixture.

General procedure for the synthesis of (1Z,1'Z)-1-(4-bromophenyl)-2-((2-(((Z)-2-(4-bromophenyl)-2-(hydroxyimino) ethyl)thio)ethyl)thio)ethanone oxime (13)[25]:

In a 100-mL two necked round bottom flask, 2,2'-(ethane-1,2-diylbis(sulfanediyl))bis(1-(4-bromophenyl)ethanone) (**6a**)(10.0 mmol) and hydroxyl ammonium chloride ($NH_2OH.HCl$) **(11)** (40.0 mmol) are dissolved in ethanol (20 mL) and then NaOAc (30.0 mmol w.r.t $NH_2OH.HCl$) is added. Then, the reaction mixture is stirred at reflux temperature for 2h. The progress of the reaction is monitored by TLC. After completion of the reaction, reaction mixture is cooled to RT and then filtered, washed thoroughly with ethanol. The filtrate is collected and the solvent is removed under reduced pressure. To the crude reaction mass, water (25 mL) is added and the product **(13)** is extracted with EtOAc (2x10 mL). Then the organic layer is collected and washed with water (2x25 mL) twice, dried over anhydrous $MgSO_4$ and the solvent is removed under reduced pressure. The crude product (**13)** is recrystallized from the ethanol (5mL) and n-hexane (15 mL) mixture. The same experimental procedure is followed for the preparation of (1Z,1'Z)-2-((3-(((Z)-2-(hydroxyimino)-2-(naphthalen-2-yl)ethyl)thio)propyl)thio)-1-(naphthalen-2-yl)ethanone oxime (**14**) from 2,2'-(propane-1,3-diylbis(sulfanediyl))bis(1-(naphthalen-2-yl)ethanone) (**6l**).

Experimental procedure for the synthesis of (2Z,10Z)-3,10-bis(4-bromophenyl)-1,12-dioxa-5,8-dithia-2,11-diazacyclotetradeca-2,10-diene (15)[26]:

In a 100-mL two necked round bottom flask, compound **13** (10.0 mmol) is dissolved in DMSO (15 mL). The reaction mass is cooled to 5 to 10°C. At this temperature, aqueous KOH solution (20.0 mmol of KOH is dissolved in 5 mL of water) is added slowly and stirred at 5 to 10°C for 15 min. Then, 1, 2-dibromoethane (**1v**) (10.0 mmol) is taken in 10 mL of DMSO and is added slowly at 5 to 10°C and the reaction mass is stirred at the same temperature for 10 min. The reaction progress is monitored by TLC. After completion of the reaction, the reaction mixture is quenched in crushed ice and then the product (**15**) is extracted with diethyl ether (2x15 mL) twice. The solvent is then evaporated under reduced pressure. The obtained crude product (**15**) is purified by column chromatography using silica gel (99:1 ratio of n-hexane and ethyl acetate).

General experimental procedure for gram scale (25g scale) synthesis:

A mixture of 4-bromo phenacyl bromide (**1k**) (9.0 mol), 2-mercaptobenzothiazole (**2a**) (9.0 mol) and ZnO (10.0% w/w) is taken in a large porcelain bowl and ground together with a pestle for 5 min at 25-30°C. After completion of the reaction, the crude mass is washed with water (2x50 mL) twice and extracted with ethyl acetate (2x25 mL) twice. Then the catalyst is separated by filtration under vacuum. The organic layer is washed with water, dried with anhydrous $MgSO_4$ and the solvent is evaporated under reduced pressure. The obtained product (**3k**) is purified by recrystallization using ethanol.

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Keywords: Mechanochemical synthesis, C-S bond construction, Phenacyl/benzyl/alkyl bromides, Thiols, ZnO.

Supporting information available: Physical and spectral (^{1}H and ^{13}C NMR and HRMS) data of the synthesized compounds. See doi:

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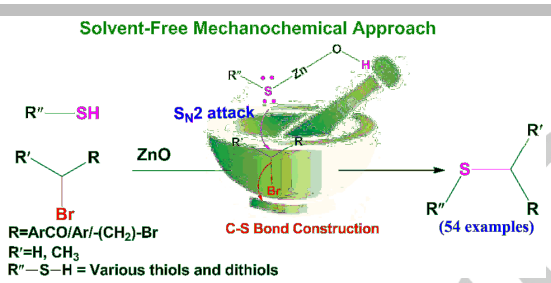
FULL PAPER

Zinc oxide-catalyzed solvent-free mechanochemical route has been developed for the rapid construction of C-S bond using a variety of thiols and phenacyl/benzyl/alkyl bromides *via* a nucleophilic substitution.



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Zinc oxide-Catalyzed Solvent-Free Mechanochemical Route for C-S Bond Construction: A Sustainable Process