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Straightforward Synthesis of Novel Substituted 1,3,4-Thiadiazole Derivatives in Choline Chloride-Based Deep Eutectic Solvent

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ABSTRACT

A one-pot, three-component route for the synthesis of novel 1,3,4-thiadiazole derivatives using a ketene *S*,*S*-acetal, a carbonyl compound and thiocarbohydrazide is described. The main advantages of this approach are high yields, short reaction times, simple reaction conditions and a green reaction medium. The 1,3,4-thiadiazole core has been substituted with biologically active groups such as arylhydrazones, coumarin, isatin, Meldrum's acid and barbituric acid. Structures of the thiadiazoles were elucidated from spectroscopic data.

Amongst heterocyclic compounds, those containing five-membered rings are the most commonly encountered building blocks, with a large number possessing interesting biological activities.[1] Thiadiazoles consist of four isomers; 1,2,3-thiadiazoles, 1,2,4-thiadiazoles, 1,2,5-thiadiazoles, and 1,3,4-thiadiazoles (Fig. 1a), of which 1,3,4-thiadiazoles have seen special interest in recent years demonstrating biological properties including antimicrobial,[2] antiviral,[3] antitubercular,[4] antiparasitic,[5] anticonvulsant,[6] antidepressant, anxiolytic,[7] and anticancer[8] activities. They are also key intermediates in the synthesis of commercially available drugs such as megazol,[9] acetazolamide, and furidiazine (Fig. 1b).[10]

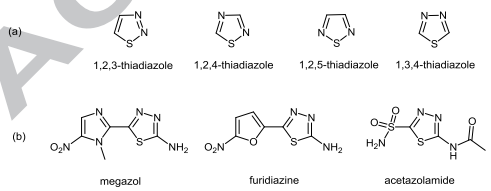

Figure 1. (a) Isomers of thiadiazole. (b) Commercially available 1,3,4-thiadiazole based drugs.

Commonly reported methods for the synthesis of 1,3,4-thiadiazoles include those starting from acylhydrazines, including monoacylhydrazines and *N*,*N*′-diacylhydrazines,[11] or thiosemicarbazides,[12] thiocarbazides,[13] dithiocarbazates,[14] thiohydrazides and bithioureas,[15] as well as the transformation of 1,3,4-oxadiazoles.[16] These methods usually require a sulfuration reagent to introduce the sulfur atom to the ring, a cyclization reagent, or a combination of reagents to form the thiadiazole ring. Additionally, commonly reported methods often suffer from harsh reaction conditions, multi-step procedures, or stoichiometric formation of intractable by-products.[17]

A one-pot or one-step synthesis *via* simple and efficient procedures would be interesting for both laboratory and industrial purposes.[18] Herein, a one-pot approach for the synthesis of novel substituted 1,3,4-thiadiazoles using thiocarbohydrazide, a carbonyl compound and a ketene *S*,*S*-acetal in a deep eutectic solvent (DES) was developed (Scheme 1).

DESs are commonly prepared from a eutectic mixture of Lewis or Brønsted acids and bases, which may contain a variety of anionic or cationic species, and possess a melting point much lower than either of the individual components.[12] Compared to ionic liquids, DESs are generally cheaper to make, are less toxic and are often biodegradable. Thus, DESs can be used as low–cost, safe and efficient solvents.[13]. Herein, the choline chloride and urea based DES (ChCl-urea) was used.

Our investigation started with the one-pot, three-component model reaction of thiocarbohydrazide **1**, Meldrum's acid based ketene-*S*,*S*-acetal **3a** or barbituric acid based ketene-*S*,*S*-acetal **3b** and 4-methoxybenzaldehyde in order to optimize the reaction conditions. First, the effects of various solvents on reaction times and yields were evaluated. Moderate to high yields of **4a** and **5a** were obtained in both protic and aprotic solvents (Table 1, Entries 1-5 and 14-18). Since DESs have many advantages including ready availability, non-toxicity, biodegradability, recyclability, and low price in comparison with organic

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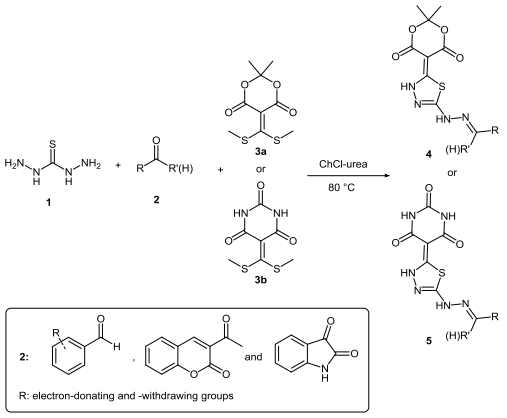
solvents,[19] the synthesis of the model compounds were also investigated in ChCl-urea.



Scheme 1. One-pot synthesis of 1,3,4-thiadiazoles

Although poor yields were obtained at room temperature (Entries 6 and 19), increasing the temperature to 80 °C resulted in increased yields (Entries 7-9 and 20-22). Further increasing the reaction temperature to 95 °C resulted in decreased yields (Entries 10 and 23). Finally, the synthesis of **4a** and **5a** in mixtures of EtOH or MeOH and ChCl-urea were examined. Although the yields increased upon increasing the amount of ChCl-urea in the reaction medium, the yields were lower compared to those using only ChCl-urea as the reaction medium.

Table 1. Reaction conditions optimization for the synthesis of **4a** and **5a**.

Entry	Product	Solvent/Co-solvent[b]	Temp. (°C)	Time (h)	Yield[a] (%)
1	**4a**	EtOH	Reflux	5	65
2	**4a**	MeOH	Reflux	5	45
3	**4a**	CH_3CN	Reflux	5	35
4	**4a**	DMF	100	5	50
5	**4a**	CH_2Cl_2	Reflux	5	50
6	**4a**	ChCl-urea	rt	5	-
7	**4a**	ChCl-urea	45	5	35
8	**4a**	ChCl-urea	65	5	50
9	**4a**	**ChCl-urea**	**80**	**5**	**85**
10	**4a**	ChCl-urea	95	5	65
11	**4a**	EtOH/ChCl-urea (10 mol%)	80	5	45
12	**4a**	EtOH/ChCl-urea (20 mol%)	80	5	55
13	**4a**	EtOH/ChCl-urea (30 mol%)	80	5	65
14	**5a**	EtOH	Reflux	5	40
15	**5a**	MeOH	Reflux	5	70
16	**5a**	CH_3CN	Reflux	5	40
17	**5a**	DMF	100	5	50
18	**5a**	CH_2Cl_2	Reflux	5	45
19	**5a**	ChCl-urea	rt	5	-
20	**5a**	ChCl-urea	45	5	43
21	**5a**	ChCl-urea	65	5	50
22	**5a**	**ChCl-urea**	**80**	**5**	**80**
23	**5a**	ChCl-urea	95	5	60
24	**5a**	MeOH/ChCl-urea (10 mol%)	65	5	48
25	**5a**	MeOH/ChCl-urea (20 mol%)	65	5	52
26	**5a**	MeOH/ChCl-urea (30 mol%)	65	5	67

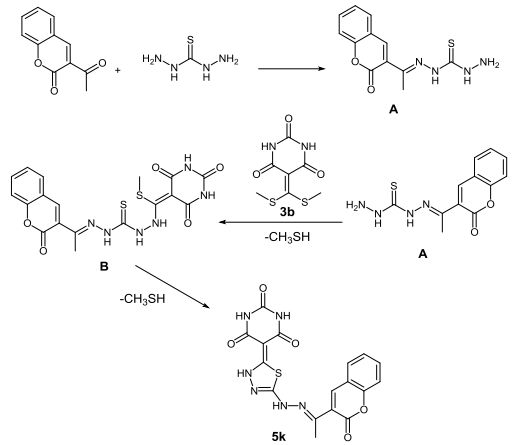
[a] Isolated yield

[b] Solvent volume (10 mL)

Thus, heating thiocarbohydrazide **1** (0.4 mmol), carbonyl compound **2** (0.4 mmol) and ketene-*S*,*S*-acetal **3a** or **3b** (0.4 mmol) in ChCl-urea at 80 °C was considered as the optimum conditions for the synthesis of products **4** and **5**.[20]

The scope of the reaction was then examined using various carbonyl compounds (Table 2). Using this method, 24 derivatives were synthesized in moderate to high yields. Aromatic aldehydes containing electron-withdrawing groups such as 4-chloro-3-nitrobenzaldehyde, 2,6-dichlorobenzaldehyde, 2,4-dichlorobenzaldehyde and 3-nitrobenzaldehyde proceeded with high yields (Entries 3–6 and 15-17). Aromatic aldehydes containing electron-donating groups such as 3-methoxybenzaldehyde, 4-methoxybenzaldehyde, 4-(dimethylamino) benzaldehyde and 2-hydroxybenzaldehyde also afforded comparative yields (Entries 1, 2, 7, 10, 12, 13, 14, 19 and 22). Furthermore, 5-membered heterocyclic aldehydes such as furan-2-carbaldehyde and thiophen-2-carbaldehyde were suitable substrates (Entries 8, 9, 20 and 21). Due to the considerable biological significance of the isatin and coumarin motifs, 3-acetylcoumarin and isatin were applied as carbonyl compounds to give the desired products in high yields (Entries 11, 12, 23 and 24).

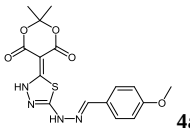
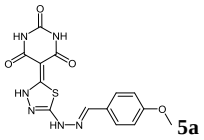
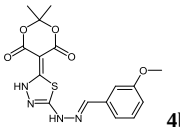
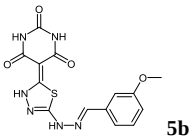
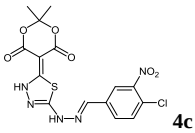
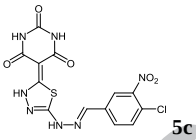
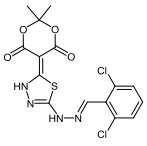
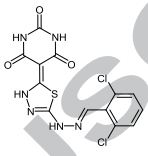
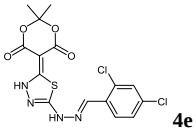
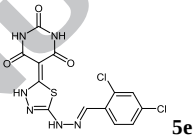
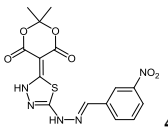
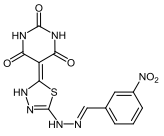
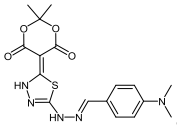
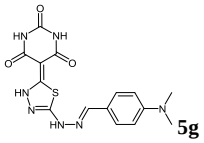
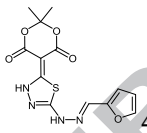
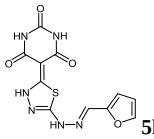
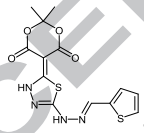
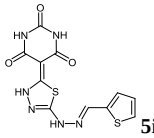
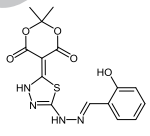
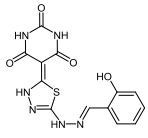
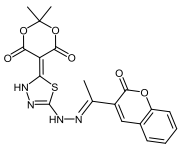
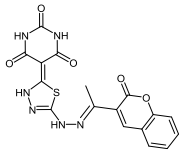
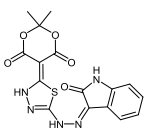
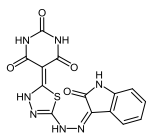
The proposed mechanism for the synthesis of compounds **4** and **5** is exemplified for compound **5k** (Scheme 2). The reaction begins with the reaction of thiocarbohydrazide with 3-acetyl-coumarin to give the corresponding thiocarbohydrazone **A**. Then, condensation of thiocarbohydrazone **A** with ketene-*S*,*S*-acetal **3b** occurs over two sequential steps; first, aza-Michael addition of the thiocarbohydrazone nitrogen to the ketene-*S*,*S*-acetal, followed by elimination of methanethiol to provide intermediate **B**, which undergoes intramolecular cyclization and elimination of the second methanethiol group to afford **5k**. [21]



Scheme 2. Proposed mechanism for the synthesis of 1,3,4-thiadiazoles

In conclusion, a simple and efficient method has been developed for the synthesis of novel molecules containing the 1,3,4-thiadiazole ring using a one-pot, three-component reaction of a carbonyl compound, thiocarbohydrazide, and a ketene-*S*,*S*-acetal. The products were obtained in high yields in suitable times using ChCl-urea as a green reaction medium. This protocol provides a straightforward route for the synthesis of complex molecules containing biologically active motifs such as 1,3,4-thiadiazole, Meldrum's acid or barbituric acid, and coumarin, isatin or substituted benzenes in a single molecule which may find interest for the construction of novel pharmaceuticals.

Table 2. Diversity in the synthesis of 1,3,4-thiadiazole derivatives **4a–l** and **5a-l**[a]

Entry	Product	Time (h)	Yield (%)[b]	Entry	Product	Time (h)	Yield (%)[b]
1	 **4a**	5	85	13	 **5a**	5	80
2	 **4b**	4	80	14	 **5b**	4.5	85
3	 **4c**	5	67	15	 **5c**	5	65
4	 **4d**	6	55	16	 **5d**	5.5	68
5	 **4e**	4.5	60	17	 **5e**	6.5	70
6	 **4f**	6	67	18	 **5f**	5.5	65
7	 **4g**	5.5	80	19	 **5g**	5	83
8	 **4h**	4	65	20	 **5h**	6	70
9	 **4i**	4.5	70	21	 **5i**	5.5	65
10	 **4j**	5	80	22	 **5j**	4.5	80
11	 **4k**	4	65	23	 **5k**	6	75
12	 **4l**	6	70	24	 **5l**	5.5	65

[a] Reagents and conditions: Meldrum's acid based ketene-*S*,*S*-acetal **3a** or barbituric acid based ketene-*S*,*S*-acetal **3b** (1 mmol), thiocarbohydrazide **1** (1 mmol), carbonyl **2** (1 mmol), ChCl-urea (20 mL), 80 °C.

[b] Isolated yields.

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20. Typical procedure for the synthesis of compound **4a**: 4-Methoxybenzaldehyde (0.4 mmol) was added to a stirred solution of thiocarbohydrazide **1** (0.4 mmol) in ChCl-urea (10 mL) over 30 min and stirring continued at room temperature for 1 h. Then, 5-[bis(methylthio)methylene] Meldrum's acid **3a** (0.4 mmol) was added and the reaction mixture heated at 80 °C for specified time in Table 2. After reaction completion, ice water was added and the precipitate collected and recrystallized from ethyl acetate to give the desired product **4a** as a yellow solid; 85% isolated yield. IR (KBr): 3396, 3245, 3003, 2836, 1689, 1639 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 13.40 (s, 1H), 12.27 (s, 1H), 7.97 (s, 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.00 (d, *J* = 8.3 Hz, 2H), 3.77 (s, 3H), 1.61 (s, 6H). ^{13}C NMR (75MHz, DMSO-d_6): δ = 162.3, 161.1, 160.6, 159.7, 143.6, 128.1, 126.2, 114.4, 103.3, 76.5, 55.3, 26.0. Anal. calcd for $C_{16}H_{16}N_4O_5S$: C, 51.06; H, 4.28; N, 14.89. Found: C, 51.02; H, 4.38; N, 14.80.
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Straightforward Synthesis of Novel Substituted 1,3,4-Thiadiazole Derivatives in Choline Chloride-Based Deep Eutectic Solvent

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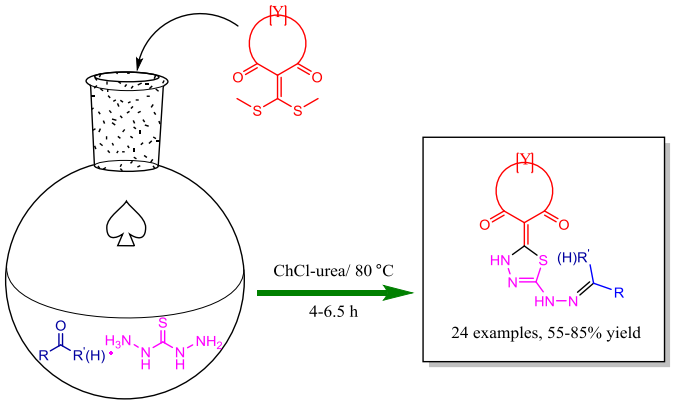

HIGHLIGHTS

- ✓ One-pot, three-component route for the synthesis of novel 1,3,4-thiadiazoles.
- ✓ Choline Chloride-Based Deep Eutectic Solvent used as a green reaction medium.
- ✓ Advantages of this work include high yields and simple reaction condition.
- ✓ Products contain biologically active motifs.