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Solvent Free Green Synthesis of Azines and Their Conversion to 2,5-Disubstituted-1,3,4-thiadiazoles

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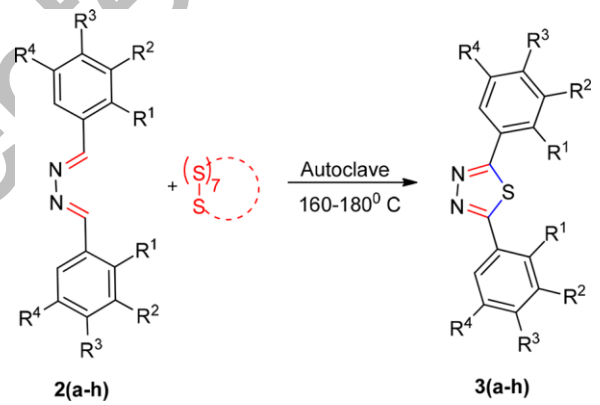
Abstract

A solvent-free, clean and efficient method has been developed for the synthesis of 2,5–disubstituted–1,3,4–thiadiazoles *via* azines. This approach exploits the synthetic potential of clean reaction and offers many advantages such as excellent product yields, easy isolation of products and eco-friendly benign reaction conditions. The newly synthesized compounds were analyzed by IR, ^{1}H NMR, ^{13}C NMR and elemental analysis.



KEYWORDS: azine, 1,3,4–thiadiazole, solvent free, green synthesis, autoclave

1. INTRODUCTION

Due to the amplifying concern for the adverse influence of organic solvents on the environment, solvent-free organic reactions have attracted the attention of organic chemists.[1] Green chemistry has been widely used in the current chemical research to develop new protocol that is less hazardous to human health and to the environment has received extensive attention.[2,3] The tremendous increase in Environmental (E)-factor[4] in pharmaceutical industry than in other industry sector is mainly due to the use of solvents[5] in many batch process.[6] Therefore, it is essential to contrive solvent-free methodologies[7] for the eco-friendly, greener[8] synthesis of drugs.

1,3,4–Thiadiazoles are important heterocycles with "N–C–S" linkage which can work as the active center, chelate certain metal ions *in vivo*, and show good tissue permeability. The lower toxicity and *in vivo* stability of thiadiazole nucleus is attributed to its aromaticity.[9] Thiadiazoles have exhibited potential antiviral,[10] anticancer,[11] anti-inflammatory,[12] antibacterial,[13] analgesic,[14] antiglaucoma[15] and fungicidal activities.[16] Recently in our lab Rai *et al*., have developed the solvothermal method for the synthesis of thioesters and thioamides,[17] isoxazoles and pyrazoles,[18] for the conversion of oxadiazoles to thiadiazoles[19] and aldehyde semicarbazones to bishydrazones.[20]

The different synthetic pathways employed to prepare azines[21] and 1,3,4–thiadiazoles have been reported. The most common procedure for the synthesis of 1,3,4–thiadiazoles involves the cyclization of 1,2–diacylhydrazines or its thia–analogues in presence of

$SOCl_2$ or $POCl_3$.[22] Symmetrical 2,5–disubstituted–1,3,4–thiadiazoles were synthesized by condensation of various aldehydes and hydrazine under the pressure of H_2S using microwave irradiation. The major drawback of the above said method was, it needs additional purification step for the removal of H_2S obtained as byproduct and extra care must be taken for the controlled release of H_2S.[23] The 1,3,4–thiadiazoles were also synthesized from the corresponding 1,4–dicarbonyl or acyl precursors using P_2S_5 and Lawesson's reagent,[24] from pentafluorophenyl esters,[25] acid hydrazides and triethylorthoalkanoates[26] and by the oxidation of *in situ* generated thiosemicarbazones.[27]

The antecedent techniques though afford multitude of choices to conspire substituted 1,3,4–thiadiazoles, suffer from longer reaction time, exhaustive work-up, low yield and multistep procedures, which has restricted the exertion of these methods in high throughput synthesis. Thus an improved, economical, swift and solvent free access to substituted 1,3,4–thiadiazoles is of current interest to organic chemists.

2. RESULTS AND DISCUSSION

Owing to the competence and continuation of our interest in autoclave reactions, here we communicate the novel method for the synthesis of azines starting from semicarbazones (Scheme 1) and their conversion to 2,5–disubstituted–1,3,4–thiadiazole *via* sulfuration of substituted azines under solvent free condition in high yield Scheme 3.

The formation of azines (**iv**) from semicarbazones (**i**) presumably occur *via* the elimination of bisurea (**v**) from the two semicarbazone molecule[20] Scheme 2. Finally the

azines were treated with elemental sulphur under solvothermal conditions to get 1,3,4–thiadiazoles in 85–95% yield as shown in Scheme 3.

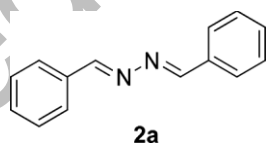
The probable mechanism for the formation of 2,5–disubstituted–1,3,4–thiadiazole **(3)** from azine (**a**) involves following steps. Initially the azine **(a)** attacks the sulfur in the S8 (α sulphur) form which results in the ring opening of α sulphur yields the intermediate (**b**). Later the *in situ* generated intermediate (**b**) cyclizes to give intermediate (**c**). The intermediate (**c**) undergoes dehydrogenation by sulphur to yield 2,5–disubstituted–1,3,4–thiadiazole (**3**). The reason for the dehydrogenation may be attributed to the presence of high temperature and pressure in autoclave reactions and acquisition of aromaticity in the final product Scheme 4.

The structural assignments to newly synthesized compounds **2**(**a**–**h**) and **3**(**a**–**h**) was based on their elemental analysis and spectral (IR, ^{1}H NMR, ^{13}C NMR and Mass) data. The IR spectra of the compound **2a** showed the absence of amide carbonyl absorption band at 1650 cm^{-1} to 1750 cm^{-1} and –NH peak at 3400 cm^{-1} to 3200 cm^{-1} and showed new peak due to C═N at 1645 cm^{-1}. In the ^{1}H NMR spectra the signals of the newly synthesized compounds were verified on the basis of their chemical shifts, multiplicities, and coupling constants. The formation of compound **2a** was confirmed by the disappearance of peak at δ 6.7 and 7.9 due to –NH and $–NH_2$. In ^{13}C NMR spectra, appearance of a doublet at δ 161.0 ppm due to C═N substantiated the formation of compound **2a**.

The IR spectra of the compound **3a** showed the appearance of a new peak at 670 cm^{-1} due to C–S stretching. The IR spectra of all other synthesized compounds showed characteristic signals at 1640–1595 cm^{-1} for (C═N) and 1570–1460 cm^{-1} for (C═C). In ^{1}H NMR spectra, disappearance of peak at δ 8.9 due to –CH═N and in ^{13}C NMR appearance of peaks at δ 174.1 ppm due to C–S linkage confirms the formation of cyclized heterocycle **3a**. The aryl moiety exhibited characteristic signals in the aromatic region of the spectrum. The mass spectrum of all the compounds showed molecular ion peak at M+1 corresponding to its molecular formula, which confirmed its chemical structure.

3. EXPERIMENTAL SECTION

General Procedure For The Synthesis Of Bishydrazones (1E, 2E)-1,2-Dibenzylidenehydrazine (2a)



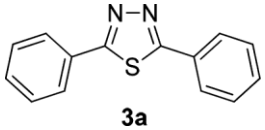
2a

(*E*)-2-benzylidenehydrazinecarboxamide (**1a,** 1g, 6.13 mmol) was taken in a autoclave reaction container (Teflon Liner). The lid was placed and was lowered into the autoclave, the plates were kept over it and the autoclave was closed and tightened. It was kept in the oven at 160-180°C for 4-6hr. The products after cooling, were extracted into diethyl ether (20 mL), washed thoroughly with water. TLC of the solution shows single spot, which was different from the starting material. The organic layer was dried over anhydrous Na_2SO_4, solvent was evaporated under reduced pressure and the product obtained as yellow crystalline solid in 90% yield (1.15 g), mp 89-92°C (lit 88-89°C).[27] IR cm^{-1}

(Nujol): 1645 cm^{-1} (C=N); ^{1}H NMR (400 MHz, $CDCl_3$), δ ppm (*J*, Hz): 7.48-7.54 (m, 6H), 7.88-7.91 (d, 4H, *J* = 7.2), 8.72 (s, 2H); ^{13}C NMR (100MHz $CDCl_3$): δ (ppm) 129.1, 129.7, 132.4, 137.3, 161.0; MS (relative intensity): m/z for $C_{14}H_{12}N_2$; 209.2 $[M+H]^+$ (100) Anal. % Calc: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.68; H, 5.85; N, 13.49.

The same procedure was followed in all the case.

General Procedure For The Synthesis Of 2,5-Disubstituted-1,3,4-Thiadiazole (3a)



3a

(1*E*, 2*E*)-1,2-dibenzylidenehydrazine (**2a,** 1g, 4.80 mmol) and sulphur (0.08g, 2.40 mmol) was taken in an autoclave reaction container (Teflon Liner). The lid was placed and was lowered into the autoclave, the plates were kept over it and the autoclave was closed and tightened. It was kept in the oven at 160°-180°C for 4-6hr. The products obtained after cooling, were extracted into diethyl ether (20mL), washed thoroughly with water. TLC of the solution shows single spot, which was different from the starting material. The organic layer was dried over anhydrous sodium sulphate; solvent was evaporated under reduced pressure and the product obtained as yellow crystalline solid in 90% yield (1.03g), mp 144-146 °C (lit mp = 143-144°C). IR cm^{-1} (Nujol): 1648 cm^{-1} (C=N) and 670 cm^{-1} (C-S); ^{1}H NMR (400 MHz, $CDCl_3$), δ ppm (*J*, Hz): 7.50-7.56 (m, 6H), 7.89-7.95 (d, 4H, *J* = 8.8); ^{13}C NMR (100 MHz $CDCl_3$): δ (ppm) 128.7, 129.2, 130.9, 133.5, 174.1; MS (relative intensity): m/z for $C_{14}H_{10}N_2S$; 238.9 $[M+H]^+$ (100); Anal. % Calc: C, 70.56; H, 4.23; N, 11.76; Found: C, 70.53; H, 4.25; N, 11.77.

The same procedure was followed in all the case.

4. CONCLUSIONS

In conclusion we have developed a novel protocol for the synthesis of azines and their conversion to 2,5–disubstituted–1,3,4–thiadiazoles. The benefit of the described reaction is the atom efficiency. It only requires theoretical amount (0.5 eq) of elemental sulfur, and H_2 gas is the only waste that is produced during the reaction. Also the present method offers many advantages such as excellent product yields, easy isolation of products and eco-friendly benign reaction conditions.

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SUPPLEMENTAL MATERIAL

Supplementary data (Experimental details, NMR, MS and elementary analysis) for this article can be accessed on the publisher's website.

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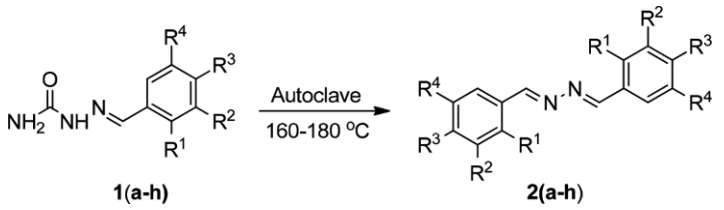
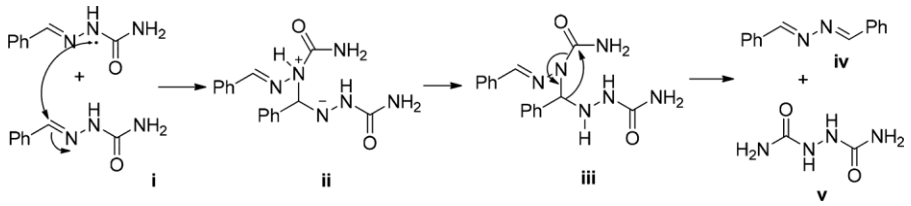
Scheme 1 Synthesis of azines

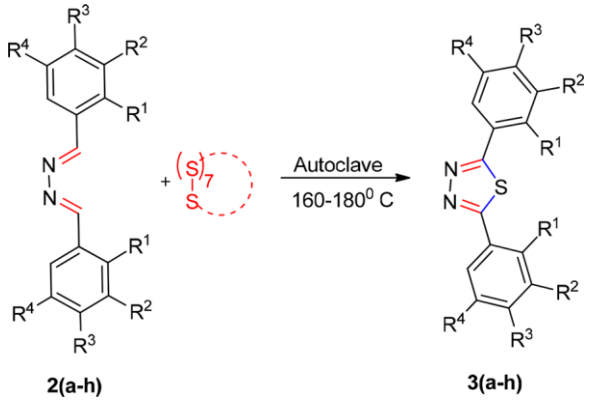


1(a-h) 2(a-h)

Scheme 2 The possible mechanism for the conversion of semicarbazone to azine.



Scheme 3 Synthesis of 2,5–disubstituted–1,3,4–thiadiazole.



Scheme 4 The possible mechanism for the conversion of azine to 2,5-disubstituted-1,3,4-thiadiazole.