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Multi-component synthesis of 1,2-diphenyl-2-[2-(5-aryl-6*H*-1,3,4-thiadiazin-2-yl)hydrazono] ethanone

Abstract: The reaction of thiocarbohydrazide with benzil and a substituted phenacyl bromide provides a facile synthetic route to a 1,2-diphenyl-2-[2-(5-aryl-6*H*-1,3,4-thiadiazin-2-yl)hydrazono]ethanone. The synthesized compounds were characterized by spectral and analytical data.

Keywords: benzyl; 1,2-dicarbonyls; multi-component reactions; 1,3,4-thiadiazine; thiocarbohydrazide.

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Introduction

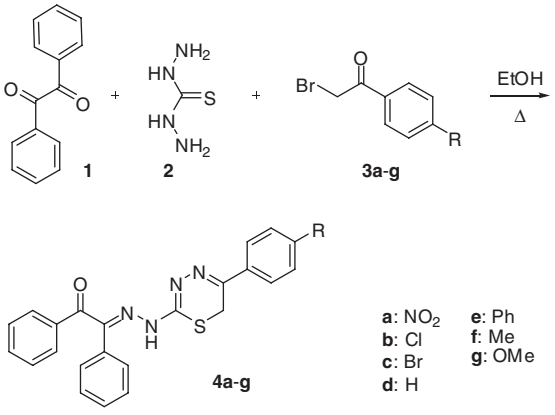
In recent times, thiocarbohydrazide and its derivatives have attracted much attention due to their applications in the synthesis of heterocyclic compounds [1, 2], in the synthesis of transition metal complexes [3], and in pharmacological studies [4]. Compounds containing 1,3,4-thiadiazines are biologically active. Many of these derivatives are used as cardiotonic and hypertensive agents [5, 6], and can also be used for the treatment of tumors and acquired immunodeficiency syndrome (AIDS) [7]. They are widely used as nematicides, fungicides, herbicides, and insecticides [8]. Some of the thiadiazine derivatives are active against *Trypanosoma cruzi* amastigotes [9].

Earlier work [10] has shown that the reaction of thiocarbohydrazide or its substituted analogs with 1,2-dicarbonyl compounds is complex and leads to various condensation products of linear and cyclic structures [11–15]. The product depends on the structure of the reacting materials and the reaction conditions. A similar observation has also been reported for the reaction of carbohydrazide with 1,2-dicarbonyl compounds [16]. A variety of products have been reported [10, 17].

Multi-component reactions (MCRs) have gained considerable interest recently, as part of green chemistry and from an economic point of view. Such reactions have intrinsic advantages, such as simplicity, good atom and step economy, minimum energy consumption, producing little waste and being highly selective [18–21]. Prompted by the earlier reports mentioned above and the significant biological activities of sulfur and nitrogen heterocycles, we became interested in work on thiocarbohydrazide. The three-component reaction of thiocarbohydrazide with benzil and an α-haloketone is described in this report.

Results and discussion

Equimolar amounts of benzil, thiocarbohydrazide, and a phenacyl bromide were condensed in ethanol under reflux conditions to give 1,2-diphenyl-2-[2-(5-aryl-6*H*-1,3,4-thiadiazin-2-yl)hydrazono]ethanone **4** in good yield (Scheme 1). In light of the reported literature on analogous reactions, there could have been the formation of substituted products **6** and/or **8** via intermediate product **5** (Scheme 2). These compounds were not found and the structure of



Scheme 1 Synthesis of 1,2-diphenyl-2-[2-(5-aryl-6*H*-1,3,4-thiadiazin-2-yl)hydrazono] ethanone.

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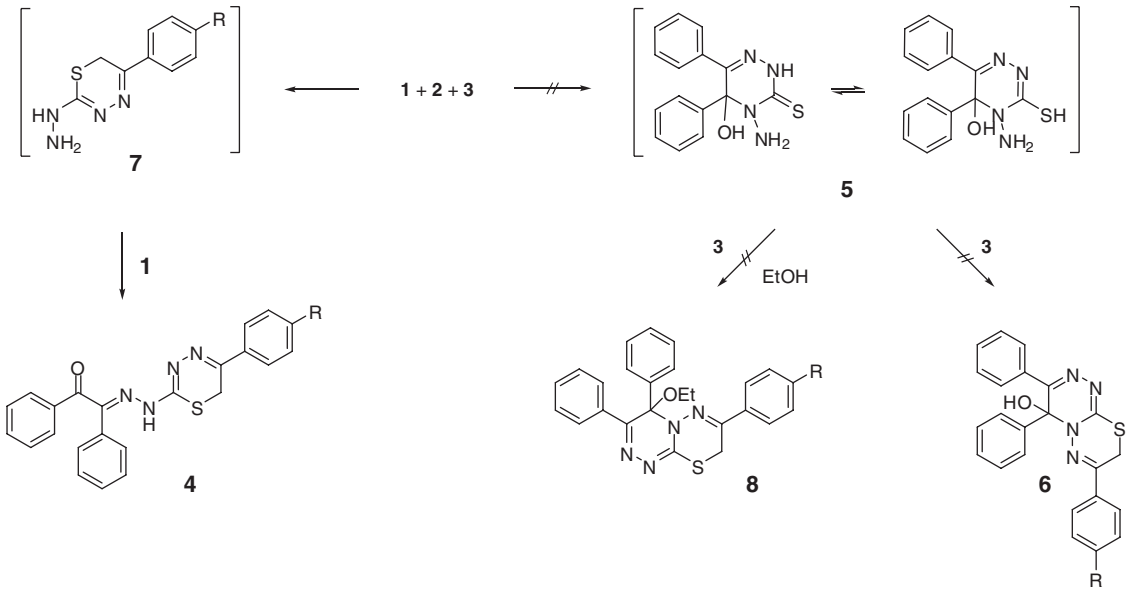

Scheme 2 The plausible pathway for the reaction.

isolated products **4a–g** were unequivocally shown by analysis of their spectral data and elemental analysis.

These results reveal that the thiadiazine ring of **4** is formed more readily than the triazine rings of the hypothetical products **6** and **8**. It can be suggested that the initial reaction of thiocarbohydrazide with a phenacyl bromide generates the intermediate product **7** preferably and the hypothetical compound **5** is not formed. Then the hydrazino group of the intermediate compound **7** thus formed undergoes condensation with one of the C=O group of benzil to give the end product **4**.

Conclusion

In contrast to the suggestions of literature reports, the reaction of thiocarbohydrazide with benzyl and a phenacyl bromide yields a 1,3,4-thiadiazine derivative.

Experimental

Thiocarbohydrazide was prepared according to a modified literature procedure [22]. Other reagents and solvents were procured from commercial sources. They were used without further purification. Melting points were determined in open capillaries on a Stuart SMP-30 melting point apparatus and are uncorrected. The CHNS elemental analyses were performed by a Carlo Erba EA 1108 automatic elemental analyzer. The purity of the compounds was checked using TLC plates. IR spectra (KBr) were recorded on a Bruker WM-4(X) spectrometer, model 577. The ^{13}C NMR (100 MHz) and ^{1}H NMR (400 MHz) spectra were recorded in DMSO-d_6 on a Bruker WM-400 spectrometer. The electron spray ionization (ESI) mass spectra were acquired on a Perkin Elmer mass spectrometer SCIEX API- 2000 at 12.5 eV.

General procedure for the synthesis of 1,2-diphenyl-2-[2-(5-aryl-6*H*-1,3,4-thiadiazin-2-yl)hydrazono]ethanones 4a–g

A solution of benzil (**1**, 1 mmol), thiocarbohydrazide (**2**, 1 mmol), and a phenacyl bromide (**3**, 1 mmol) in ethanol (5 mL) was heated under reflux until the completion of the reaction (checked with TLC plates coated with silica gel, eluting with chloroform). The reaction mixture was then cooled, and the precipitated solid product was collected, washed with methanol, and crystallized from ethanol.

2-(2-(5-(4-Nitrophenyl)-6*H*-1,3,4-thiadiazin-2-yl)hydrazono)-1,2-diphenylethanone Reflux for 2 h; orange solid; yield 85%; mp 171–173°C; IR: 3080 (N-H), 1637 (C=O), 1522 (-C=N) cm^{-1}; ^{1}H NMR: δ 4.09 (s, 2H, S-CH$_2$- of thiadiazine), 7.44–7.46 (m, 3H, Ar-H), 7.58–7.61 (m, 4H, Ar-H), 7.69 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.81 (t, *J* = 4.1 Hz, 2H, Ar-H), 8.04 (d, *J* = 8.8 Hz, 2H, Ar-H), 8.29 (d, *J* = 8.8 Hz, 2H, Ar-H), 11.91 (s, 1H, N-H); ^{13}C NMR: δ 21.3, 123.8, 126.1, 126.9, 128.9, 129.0, 129.3, 129.4, 129.5, 130.4, 133.0, 134.4, 135.5, 140.6, 144.1, 147.5, 157.3, 197.5. Anal. Calcd for $C_{23}H_{17}N_5O_3S$ (443.48): C, 62.29; H, 3.86; N, 15.79. Found: C, 62.33; H, 3.81; N, 15.84.

2-(2-(5-(4-Chlorophenyl)-6*H*-1,3,4-thiadiazin-2-yl)hydrazono)-1,2-diphenylethanone Reflux for 2.5 h; yellow solid; yield 77%; mp 180–182°C; IR: 3065 (N-H), 1636 (C=O), 1528 (-C=N) cm^{-1}; ^{1}H NMR: δ 3.99 (s, 2H, S-CH$_2$- of thiadiazine), 7.31–7.82 (m, 14H, Ar-H), 11.66 (s, 1H, N-H); ^{13}C NMR: δ 21.5, 126.0, 127.7, 128.7, 128.9, 129.0, 129.3, 130.2, 133.1, 133.4, 134.3, 134.5, 145.7, 156.7, 163.2, 197.6. Anal. Calcd for $C_{23}H_{17}ClN_4OS$ (432.93): C, 63.81; H, 3.96; Cl, 8.19; N, 12.94. Found: C, 63.87; H, 3.78; N, 12.70.

2-(2-(5-(4-Bromophenyl)-6*H*-1,3,4-thiadiazin-2-yl)hydrazono)-1,2-diphenylethanone Reflux for 2.5 h; yellow solid; yield 82%; mp 179–181°C; IR: 3063 (N-H), 1632 (C=O), 1526 (-C=N) cm^{-1}; ^1H NMR: δ 3.99 (s, 2H, S-CH_2- of thiadiazine), 7.38–7.44 (m, 4H, Ar-H), 7.55–7.81 (m, 10H, Ar-H), 11.67, (s, 1H, N-H); ^{13}C NMR: δ 21.4, 123.1, 126.0, 127.9, 129.0, 129.0, 129.3, 130.2, 131.6, 133.1, 133.8, 134.4, 134.5, 145.8, 156.7, 163.2, 197.6; MS (ESI): *m/z* 479 [(M+1)$^+$]. Anal. Calcd for $C_{23}H_{17}BrN_4OS$ (477.38): C, 57.87; H, 3.59; N, 11.74. Found: C, 57.92; H, 3.63; N, 11.79.

1,2-Diphenyl-2-(2-(5-phenyl-6*H*-1,3,4-thiadiazin-2-yl)hydrazono) ethanone Reflux for 3.5 h; yellow solid; yield 77%; mp 184–186°C; IR: 3084 (N-H), 1640 (C=O), 1500 (-C=N) cm^{-1}; ^1H NMR: δ 3.99 (s, 2H, S-CH_2- of thiadiazine), 7.43–7.45 (m, 6H, Ar-H), 7.55–7.61 (m, 4H, Ar-H), 7.68 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.78–7.81 (m, 4H, Ar-H), 11.58 (s, 1H, N-H); ^{13}C NMR: δ 21.8, 126.0, 126.1, 128.7, 129.0, 129.3, 129.7, 130.2, 133.2, 134.4, 134.6, 147.1, 156.6, 163.6, 197.7; MS (ESI): *m/z* 399 [(M+1)$^+$]. Anal. Calcd for $C_{23}H_{18}N_4OS$ (398.48): C, 69.32; H, 4.55; N, 14.06. Found: C, 69.38; H, 4.61; N, 14.12.

2-(2-(5-([1,1′-Biphenyl]-4-yl)-6*H*-1,3,4-thiadiazin-2-yl)hydrazono)-1,2-diphenylethanone Reflux for 4 h; yellow solid; yield 75%; mp 188–190°C; IR: 3070 (N-H), 1629 (C=O), 1513 (-C=N) cm^{-1}; ^1H NMR: δ 3.95 (s, 2H, S-CH_2- of thiadiazine), 7.45–7.57 (m, 13H, Ar-H), 7.80–8.03 (m, 6H, Ar-H), 11.64 (s, 1H, N-H); ^{13}C NMR: δ 21.6, 126.0, 126.5, 126.7, 127.8, 128.0, 128.9, 129.2, 130.1, 133.1, 133.4, 133.6, 134.3, 134.5, 139.0, 141.1, 146.5, 156.5, 163.5, 197.6. Anal. Calcd for $C_{29}H_{22}N_4OS$ (474.58): C, 73.39; H, 4.67; N, 11.81. Found: C, 73.31; H, 4.73; N, 11.88.

1,2-diphenyl-2-(2-(5-(*p*-tolyl)-6*H*-1,3,4-thiadiazin-2-yl)hydrazono)ethanone Reflux for 3.5 h; yellow solid; yield 77%; mp 180–182°C; IR: 3059 (N-H), 1619 (C=O), 1518 (-C=N) cm^{-1}; ^1H NMR: δ 2.33 (s, 3H, -CH_3), 3.96 (s, 2H, S-CH_2- of thiadiazine), 7.26 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.43 (t, *J* = 3.2 Hz, 3H, Ar-H), 7.57–7.59 (m, 4H, Ar-H), 7.67–7.69 (m, 3H, Ar-H), 7.80 (t, *J* = 4.2 Hz, 2H, Ar-H), 11.52 (s, 1H, N-H); MS (ESI): *m/z* 413 [(M+1)$^+$]. Anal. Calcd for $C_{24}H_{20}N_4OS$ (412.51): C, 69.88; H, 4.89; N, 13.58. Found: C, 69.81; H, 4.84; N, 13.01.

2-(2-(5-(4-methoxyphenyl)-6*H*-1,3,4-thiadiazin-2-yl)hydrazono)-1,2-diphenylethanone Reflux for 4 h; yellow solid; yield 78%; mp 172–174°C; IR: 3051 (N-H), 1604 (C=O), 1515 (-C=N) cm^{-1}; ^1H NMR: δ 3.80 (s, 3H, -OCH_3) 3.95 (s, 2H, S-CH_2- of thiadiazine), 7.00 (d, *J* = 9.2 Hz, 2H, Ar-H), 7.36–7.43 (m, 5H, Ar-H), 7.57–7.59 (m, 3H, Ar-H), 7.73–7.81 (m, 4H, Ar-H), 11.46 (s, 1H, N-H); ^{13}C NMR: δ 21.8, 55.2, 114.0, 125.9, 126.9, 127.6, 128.6, 129.0, 129.3, 130.1, 133.2, 134.3, 134.5, 147.1, 156.1, 160.5, 164.0, 197.8; MS (ESI): *m/z* 429 [(M+1)$^+$]. Anal. Calcd for $C_{24}H_{20}N_4O_2S$ (428.51): C, 67.27; H, 4.70; N, 13.07. Found: C, 67.19; H, 4.78; N, 13.12.

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