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# A Simple and Efficient Synthesis of 3-(3-Phenyl-7*H*-[1,2,4]triazole[3,4][1,3,4]thiadiazin-6-yl)chromen-2-ones

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The compounds 3-(3-phenyl-7*H*-[1,2,4]triazole[3,4][1,3,4]thiadiazin-6-yl)chromen-2-ones (**3**), have been prepared by the condensation of 3-(2-bromoacetyl)chromen-2-ones (**1**) with 4-amino-5-phenyl-4*H*[1,2,4]triazole-3-thiols (**2**), under reflux in ethanol. A simple and efficient procedure has also been developed involving a green method wherein **3** was obtained by physical grinding of **1** with **2** in the presence of $K_2CO_3$ as base and tetrabutyl ammonium bromide as surface catalyst, in a mortar and pestle. The latter procedure has been found to be much more efficient in terms of time and yield. The structures of all the compounds have been established on the basis of their spectral and analytical data.

**Key Words: 3-(2-Bromoacetyl)chromen-2-ones, 4-Amino-5-phenyl-4*H*[1,2,4]triazole-3-thiols, Ethanol, Physical grinding.**

## INTRODUCTION

Triazole derivatives are known to possess antifungal[1,2], antibacterial[3], antiinflamatory[4], antimicrobial[5] and anti-asthamatic[6], activities. Further, it has been found that its derivatives exhibit several agricultural applications, such as herbicides[7] and insecticides[8]. On the other hand, derivatives of chromen-2-ones are also reported to show important biological activities, such as antibacterial[9], antitubercular[10], anticancer[11] and spasmolytic[12] activities. To study the combined effect of these two heterocyclic moieties in a single molecular network, we got interested in the synthesis of 3-(3-phenyl-6*H*-7-thia-2,3,4-triazainden-5-yl)chromen-2-ones (**3**).

## EXPERIMENTAL

Melting points are uncorrected and were determined in open capillary tubes in sulphuric acid bath. TLC was performed on silica gel-G and spotting was done using iodine or UV light. IR spectra were recorded using Perkin-Elmer 1000 instrument in KBr phase, $^1$H NMR on VARIAN 400 MHz instrument and Mass spectra on Agilent-LC-MS instrument giving only $M^{+\cdot}$+1 and $M^{+\cdot}$-1 values.

**General procedure for the synthesis of 3 (conventional method):** A mixture of **1** (0.5 g, 0.01 mol), **2** (0.5 g, 0.01 mol) in ethanol (25 mL) was heated under reflux for 6 h. The completion of the reaction was checked by thin layer chromatography. After the complete disappearance of the starting material spot on thin layer chromatography, the reaction mixture was cooled to room temperature and poured in ice-cold water (100 mL). The separated solid was filtered, thoroughly washed with water and dried to obtain crude product. It was recrystallized from ethanol to yield pure **3**.

**Compounds 3b:** IR (KBr, $\nu_{max}$, $cm^{-1}$): 1722 (strong, sharp, lactone carbonyl, due to coumarin ring); $^1$H NMR spectrum (DMSO-$d_6$/TMS): δ 2.23 (s, 3H -$CH_3$-), 4.30 (s, 2H, -$CH_2$-S-), 7.04-9.08 (complex, m. 9H, aryl protons), Mass: m/z 374 ($M^{+\cdot}$+1). Elemental analysis (%): Found C 67.61, H 4.08, N 11.28; $C_{21}H_{15}N_3O_2S$ requires C 67.54, H 4.05, N 11.25.

**Compounds 3c:** IR (KBr, $\nu_{max}$, $cm^{-1}$): 3380-2940 (broad, medium, bonded OH group) and at 1730 (strong, sharp lactone C=O, due to coumarin ring); $^1$H NMR spectrum (DMSO-$d_6$/TMS): δ 4.30 (s, 2H, -$CH_2$-S-), 7.02-9.10 (complex, m, 9H, aryl protons) 11.9 (s, 1H, $D_2O$ exchange -OH-), Mass: m/z 376 ($M^{+\cdot}$+1). Elemental analysis (%): Found. C 64.05, H 3.51, N 11.28; $C_{20}H_{13}N_3O_3S$ requires C 63.99, H 3.49, N 11.19.

**Compounds 3d:** IR (KBr, $\nu_{max}$, $cm^{-1}$): 3410-2980 (broad, medium OH group) and at 1741 (strong, sharp lactone C=O, due to coumarin ring); $^1$H NMR spectrum (DMSO-$d_6$/TMS): δ 2.30 (s, 3H, Ar-$CH_3$), 4.29 (s, 2H, -$CH_2$-S-),7.02-9.10 (complex, m, 8H, aryl protons), 11.42 (s, 1H, $D_2O$ exchange -OH-), Mass: m/z 390 ($M^{+\cdot}$+1). Elemental analysis (%): Found C 64.80, H 3.91, N 10.81; $C_{21}H_{15}N_3O_3S$ requires C 64.77, H 3.88, N 10.79.

**Compounds 3e:** IR (KBr, $\nu_{max}$, $cm^{-1}$): 1738 (strong, sharp, lactone carbonyl group, due to coumarin ring); $^1$H NMR spectrum (DMSO-$d_6$/TMS): δ 2.30 (s, 3H, Ar-$OCH_3$), 4.21 (s, 2H, -$CH_2$-S-),7.04-9.21 (complex, m, 9H, aryl protons), Mass: m/z 390 ($M^{+}$+1). Elemental analysis (%): Found C 64.82, H 3.93, N 10.82; $C_{21}H_{15}N_3O_4S$ requires C 64.77, H 3.88, N 10.79.

**Compounds 3f:** IR (KBr, $\nu_{max}$, $cm^{-1}$): 1720 (strong, sharp lactone carbonyl group, due to coumarin ring); $^1$H NMR spectrum (DMSO $d_6$/TMS): δ 2.30 (s, 3H, Ar-$CH_3$), 2.56 (s, 3H, Ar-$OCH_3$), 4.23 (s, 2H, -$CH_2$-S-), 7.04-9.10 (complex, m, 8H, aryl protons). Mass: m/z 404 ($M^{+}$+1). Elemental analysis (%): Found C 65.52, H 4.28, N 10.47; $C_{22}H_{17}N_3O_4S$ requires C 65.49, H 4.25, N 10.42.

**Compounds 3g:** IR (KBr, $\nu_{max}$, $cm^{-1}$): 1738 (strong, sharp lactone CO group, due to coumarin ring); $^1$H NMR spectrum (DMSO-$d_6$/TMS): δ 4.18 (s, 2H, -$CH_2$-S-),7.10-9.08 (complex, m. 8H, aryl protons), Mass: m/z 428 ($M^{+}$+1). Elemental analysis (%): Found C 56.11, H 2.63, N 9.88; $C_{20}H_{17}N_3O_3SCl_2$ requires C 56.09, H 2.59, N 9.81.

**Compounds 3h:** IR (KBr, $\nu_{max}$, $cm^{-1}$): 3255-3021 (OH), 1740 (strong, sharp lactone CO group, due to coumarin ring), 1714 (C=O); $^1$H NMR spectrum (DMSO-$d_6$/TMS): δ 2.30 (s, 3H, Ar-$CH_3$), 4.10 (s, 2H, -$CH_2$-S-), 7.04-9.12 (complex, m, 7H, aryl protons). Mass: m/z 443 ($M^{+}$+1): Elemental analysis (%): Found C 57.04, H 2.99, N 9.55; $C_{21}H_{13}N_3O_3SCl_2$ requires C 57.02, H 2.96, N 9.50.

**Alternative general procedure for the preparation of 3 (physical grinding technique):** A mixture of **1** (0.01 mol) and **2** (0.01 mol) were ground in the presence of $K_2CO_3$ (20 mM) and tetrabutyl ammonium bromide (20 mM) with a pestle in a mortar at room temperature. The completion of the reaction was monitored by TLC analysis. The mixture was treated with ice cold water (25 mL) and stirred for 10 min. The insoluble solid was filtered, washed with water and dried to obtain crude **3**. This was recrystallized from ethyl alcohol to afford the pure **3**. Physical data of compounds **3a-h** is already given above. For melting points and yields, please refer to the Table-1.

## RESULTS AND DISCUSSION

The starting compounds 3-(2-bromoacetyl)chromen-2-one[13] (**1a** *i.e.*, **1**, $R^1 = R^2$ =H) and 3-aryl-4-amino-5-mercapto-1,2,4-triazole[14] (**2a**, *i.e.*, $R^3$ = H), were synthesized according to the reported procedure. **1a** (*i.e.*, $R^1 = R^2$ = H), was condensed with **2a** (*i.e.*, $R^3$ = H), in ethanol under reflux. The reaction was found to be completed in 6 h (as seen by TLC). The product obtained, after workup, was identified to be 3-(3-phenyl-6*H*-7-thia-2,3,4-triazainden-5-yl)chromen-2-one (**3a**, *i.e.*, **3**, $R^1 = R^2 = R^3$ = H), on the basis of its spectral data. Thus, its IR spectrum in KBr, showed a strong peak at 1722 $cm^{-1}$ due to lactone C=O group, the second absorption at around 1680 $cm^{-1}$ was absent, showing the disappearance of keto carbonyl group (C=O), which was promptly seen in the IR of starting compound **1a** (*i.e.*, **1**, $R^1 = R^2$ = H). Its $^1$H NMR spectrum in DMSO-$d_6$/TMS showed signals at δ 4.2 (s, 2H, -S-$CH_2$) and at 6.99-8.89 (complex, m, 10H, aryl protons). Its mass spectrum when recorded in the CI method showed a molecular ion peak m/z $M^{+}$+1 at 360 (base peak) corresponding to a molecular mass of 359.

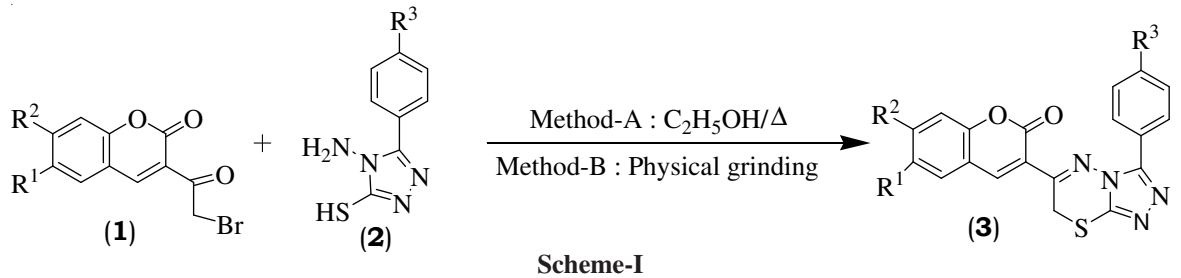
The above reaction of **1a** (*i.e.*, **1**, $R^1 = R^2$ = H), with **2a** (*i.e.*, **2**, $R^3$ = H) was found to be a general one and the other compounds namely, **3b**, (*i.e.*, $R^1 = R^2$ = H, $R^3 = CH_3$) 3-(3-*p*-tolyl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-yl)chromen-2-one, **3c** (*i.e.*, $R^1$ = OH, $R^2 = R^3$ = H), 6-hydroxy-3-(3-phenyl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-yl)chromen-2-one, **3d**, (*i.e.*, $R^1$ = OH, $R^2$ = H, $R^3 = CH_3$) 6-hydroxy-3-(3-*p*-tolyl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-yl)-chromen-2-one, **3e**, (*i.e.*, $R^1 = OCH_3$, $R^2 = R^3$ = H) 6-methoxy-3-(3-phenyl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-yl)chromen-2-one, **3f**, (*i.e.*, $R^1 = OCH_3$, $R^2$ = H, $R^3 = CH_3$) 6-methoxy-3-(3-*p*-tolyl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]-thiadiazin-6-yl)chromen-2-one, **3g**, (*i.e.*, $R^1 = R^2$ = Cl, $R^3$ = H) 6,7-dichloro-3-(3-phenyl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-yl)chromen-2-one, **3h**, ($R^1 = R^2$ = Cl, $R^3 = CH_3$) 6,7-dichloro-3-(3-*p*-tolyl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-yl)chromen-2-one, have been prepared analogously and similarly.

**3a** (*i.e.*, **3**, $R^1 = R^2 = R^3$ = H) could also be prepared by an alternative method. Thus, **1a** (*i.e.*, **1**, $R^1 = R^2$ = H) and **2a** (*i.e.*, **2**, $R^3$ = H) were ground in a mortar with the help of pestle in the presence of powdered $K_2CO_3$ and tetrabutyl ammonium bromide (TBAB) at room temperature. The product obtained on processing the solid reaction mixture was found to be identical in all respects (m.p., m.m.p. and co-TLC analysis) with **3a** obtained earlier above (**Scheme-I**).

The reaction involving grinding of solids was completed within 10 min, as shown by TLC analysis of crude mixtures. In the above reactions, $K_2CO_3$ acts as a mild base and tetrabutyl ammonium bromide as a surface catalyst. The reaction did not occur in the absence of tetrabutyl ammonium bromide even after grinding the reactants at room temperature for several hours, only in the presence of $K_2CO_3$. It thus appears that tetrabutyl ammonium bromide acts as some kind of surface

TABLE-1
PHYSICAL DATA OF COMPOUNDS **3a-h**

| Starting compounds | | Product obtained | m.p. (ºC) | Method-A (Conventional) | | Method-B (Grinding) | |
|---|---|---|---|---|---|---|---|
| 1 | 2 | | | Time (h) | Yield (%) | Time (min) | Yield (%) |
| **1a** ($R^1 = R^2$ = = H) | **2a** ($R^3$ = H) | **3a** ($R^1 = R^2 = R^3$ = H) | 212 | 6.0 | 78 | 10.0 | 80 |
| **1b** ($R^1 = R^2$ = H) | **2b** ($R^3 = CH_3$) | **3b** ($R^1 = R^2$ = H, $R^3 = CH_3$) | 217 | 5.5 | 72 | 10.0 | 81 |
| **1c** ($R^1 = R^2$ = OH) | **2a** ($R^3$ = H) | **3c** ($R^1 = R^2$ = OH, $R^3$ = H) | 248 | 6.0 | 77 | 10.3 | 80 |
| **1d** ($R^1 = R^2$ = OH) | **2b** ($R^3 = CH_3$) | **3d** ($R^1 = R^2$ = OH, $R^3 = CH_3$) | 231 | 6.0 | 70 | 10.0 | 82 |
| **1e** ($R^1 = R^2 = OCH_3$ | **2a** ($R^3$ = H) | **3e** ($R^1 = R^2 = OCH_3$, $R^3$ = H) | 221 | 5.0 | 70 | 10.2 | 80 |
| **1f** ($R^1 = R^2 = OCH_3$ | **2b** ($R^3 = CH_3$) | **3f** ($R^1 = R^2 = OCH_3$, $R^3 = CH_3$) | 247 | 5.5 | 68 | 10.0 | 80 |
| **1g** ($R^1 = R^2$ = Cl) | **2a** ($R^3$ = H) | **3g** ($R^1 = R^2$ = Cl, $R^3$ = H) | 236 | 5.5 | 72 | 10.0 | 82 |
| **1h** ($R^1 = R^2$ = Cl) | **2b** ($R^3 = CH_3$) | **3h** ($R^1 = R^2$ = Cl, $R^3 = CH_3$) | 241 | 5.0 | 77 | 10.3 | 82 |




**Scheme-I**

catalyst facilitating reactions between the reactants **1a** and **2a** in the presence of $K_2CO_3$. The results are summarized in Table-1. A comparison between the two methods shows that in the physical grinding technique the reaction time is drastically reduced and the yields are comparable.

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