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Microwave assisted, an 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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ABSTRACT

*An efficient synthesis of the title compounds 3-(3-phenyl-7H-[1,2,4]triazole[3,4][1,3,4]thiadiazin-6-yl)-chromen-2-ones (**3**), by the condensation of 3-(2-bromoacetyl)chromen-2-ones (**1**) with 4-amino-5-phenyl-4H[1,2,4]triazole-3-thiols (**2**), is being reported. The reaction has been done under conventional as well as under microwave conditions. 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.*

Keywords: 3-(2-Bromoacetyl)chromen-2-ones, 4-amino-5-phenyl-4H[1,2,4]triazole-3-thiols, ethanol and DMF.

INTRODUCTION

A survey of literature reveals that several triazole derivatives have a wide range of therapeutical properties [1-5]. They are also known to possess antiasthmatic [6], antiinflamatory [7], antimicrobial [8], antifungal [9,10], and antibacterial [11] activities. The wide spectrum of biological activities exhibited by various triazole derivatives has made them an important class of chemotherapeutic agents. Further, it has been found that several chromen-2-one derivatives exhibit important biological activities, such as anticancer [12] , antibacterial [13] and spasmolytic [14] activities. In view of the above observations and in continuation of our studies in the field of oxygen and nitrogen heterocycles of potential biological interest, the present investigation deals with the synthesis of certain chromen-2-one derivatives containing triazole moiety.

MATERIALS AND METHODS

General Conditions. 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** (0.5gm, 0.01 mol), **2** (0.5 gm, 0.01 mol) and ethanol (25 mL) was heated under reflux for 6 hr. The completion of the reaction was checked by TLC. After the complete disappearance of the starting material spot on TLC, the reaction mixture was cooled to RT and poured in to ice-cold water (100 ml). The separated solid was filtered, thoroughly washed with water and dried to obtain the crude product. The latter was recrystallized from ethanol to yield pure **3**.

3b: IR (KBr): ν 1722 cm^{-1} (strong, sharp, lactone carbonyl due to coumarin ring).; ^{1}H-NMR spectrum (DMSO-d_6/TMS): δ 2.23 (s, 3H –C**H$_3$**-), 4.30 (s, 2H, -C**H$_2$**-S), 7.04-9.08 (complex, m. 9H, **aryl protons**), Mass: m/z 374 ($M^{+\cdot}$+1):. Element. Anal: 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%.

3c: IR (KBr): ν 3380-2940 cm^{-1} (broad, medium, bonded OH group), and at 1730 cm^{-1} (strong, sharp lactone C=O, due to coumarin ring).; ^{1}H-NMR spectrum (DMSO-d_6/TMS): δ 4.30 (s, 2H, -C**H$_2$**-S), 7.02-9.10 (complex, m, 9H, **aryl protons**) 11.9 (s, 1H, D_2O exch., –O**H**), Mass: m/z 376 ($M^{+\cdot}$+1). Element. Anal: 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%.

3d: IR (KBr): ν 3410-2980 cm^{-1} (broad, medium OH group), and at 1741 cm^{-1} (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, -C**H$_2$**-S),7.02-9.10 (complex, m, 8H, **aryl protons**), 11.42 (s, 1H, D_2O exch., –O**H**), Mass: m/z 390 ($M^{+\cdot}$+1). Element. Anal: 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%.

3e: IR (KBr): ν 1738 cm^{-1} (strong, sharp, lactone carbonyl group, due to coumarin ring).; ^{1}H-NMR spectrum (DMSO-d_6/TMS): δ 2.30 (s, 3H, Ar-OC**H$_3$**), 4.21 (s, 2H, -C**H$_2$**-S),7.04-9.21 (complex, m, 9H, **aryl protons**), Mass: m/z 390 ($M^{+\cdot}$+1):. Element. Anal: 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%.

3f: IR (KBr): ν 1720 cm^{-1} (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-OC**H$_3$**), 4.23 (s, 2H, -C**H$_2$**-S),7.04-9.10 (complex, m. 8H, **aryl protons**). Mass: m/z 404 ($M^{+\cdot}$+1):. Element. Anal: Found C 65.52%, H 4.28%, N 10.47%; $C_{22}H_{17}N_3O_4S$ requires C 65.49%, H4.25%, N 10.42%.

3g: IR (KBr): ν 1738 cm^{-1} (strong, sharp lactone CO group, due to coumarin ring).; ^{1}H-NMR spectrum (DMSO-d_6/TMS): δ 4.18 (s, 2H, -C**H$_2$**-S),7.10-9.08 (complex, m. 8H, **aryl protons**), Mass: m/z 428 ($M^{+\cdot}$+1):. Element. Anal: Found C 56.11%, H 2.63%, N 9.88%; $C_{20}H_{17}Cl_2N_3O_3S$ requires C 56.09%, H 2.59%, N 9.81%.

3h: IR (KBr): ν 1740 cm^{-1} (strong, sharp lactone CO group, due to coumarin ring).; ^{1}H-NMR spectrum (DMSO-d_6/TMS): δ 2.30 (s, 3H, Ar-**CH_3**), 4.10 (s, 2H, -C**H_2**-S-), 7.04-9.12 (complex, m, 7H, **aryl protons**)3255-3021 cm^{-1} (OH), 1714 (C=O). Mass: m/z 443 ($M^{\cdot+}$+1):. Element. Anal: Found. C 57.04%, H 2.99%, N 9.55%; $C_{21}H_{13}Cl_2N_3O_3S$ requires C 57.02%, H 2.96%, N 9.50%.

Alternative general procedure for the preparation of 3 (Microwave Irradiation method): A mixture of **1** (0.01 mol) and **2** (0.01 mol) in dry DMF (10 mL) was taken in a 50 ml Erlenmeyer Flask and subjected to microwave irradiation in domestic microwave oven at 450W level for a period of 5 mints. The completion of reaction was monitored by TLC. The reaction mixture was cooled to RT and poured into ice-cold water (50 ml). The separated solid was filtered, washed with water and dried to obtain crude **3**. It was recrystallized from hexane-chloroform to obtain pure **3**. Physical data of compounds **3a-h** is already given above. For M.Pts and yields, please refer to the Table-I.

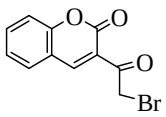
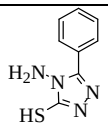
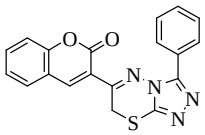
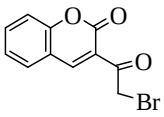
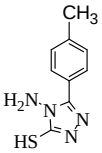
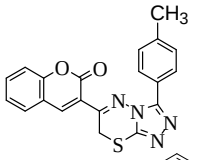
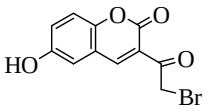
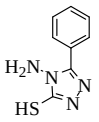
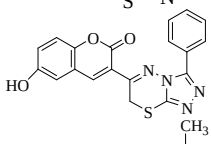
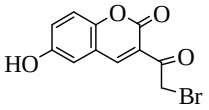
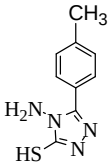
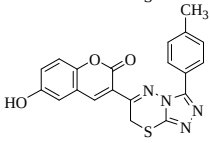
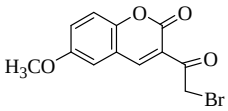
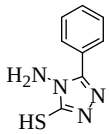
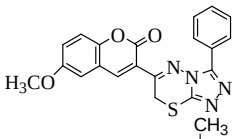
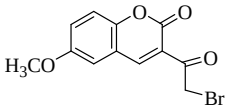
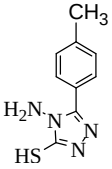
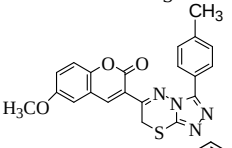
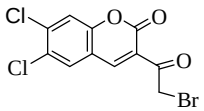
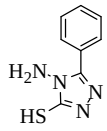
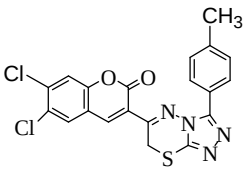
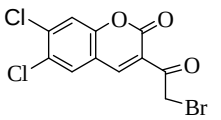
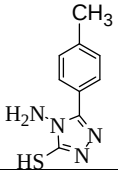
RESULTS AND DISCUSSION

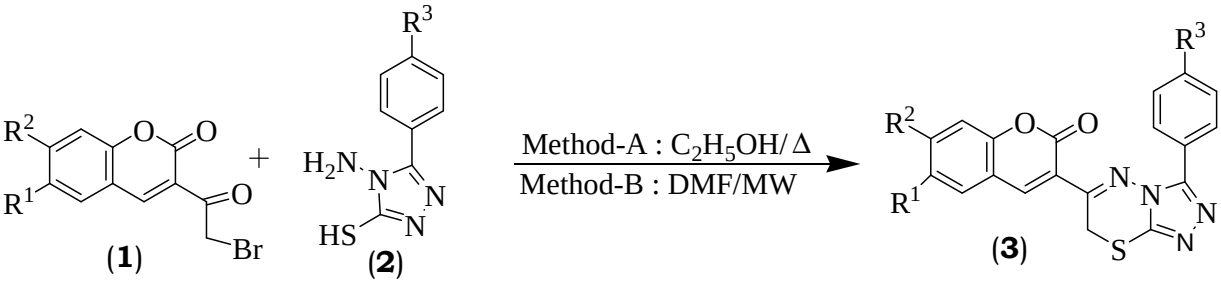
Reaction of 3-(2-bromoacetyl)-chromen-2-one[15] (**1a** i.e., **1**, R^1=R^2=H), with 3-aryl-4-amino-5-mercapto-1,2,4-triazole[16] (**2a,** i.e., R^3=H), in ethanol under reflux for 6 hrs, gave a product which has been characterized as 3-(3-phenyl-6H-7-thia-2,3,4-triazainden-5-yl)-chromen-2-one (**3a,** 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 4.20 (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 at m/z (i.e., $M^{\cdot+}$+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., **3,** R^1=R^2=H,R^3=CH_3) 3-(3-p-tolyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-yl)-chromen-2-one, **3c** (i.e., **3,** R^1=OH,R^2=R^3=H), 6-hydroxy-3-(3-phenyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-yl)-chromen-2-one, **3d**, (i.e., **3,** R^1=OH,R^2=H,R^3=CH_3) 6-hydroxy-3-(3-p-tolyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-yl)-chromen-2-one, **3e**, (i.e., **3,** R^1=OCH_3, R^2=R^3=H) 6-methoxy-3-(3-phenyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-yl)-chromen-2-one, **3f**, (i.e., **3,** R^1=OCH_3,R^2=H,R^3=CH_3) 6-methoxy-3-(3-p-tolyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-yl)-chromen-2-one, **3g**, (i.e., **3,** R^1=R^2=Cl,R^3=H) 6,7-dichloro-3-(3-phenyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-yl)-chromen-2-one, **3h**, (i.e., **3,** R^1=R^2=Cl,R^3=CH_3) 6,7-dichloro-3-(3-p-tolyl-7H-[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=H) could also be prepared by an alternative method. Thus, **1a** (i.e., **1, R^1=R^2=H**) on treating with **2** in N,N-dimethylformamide (DMF) under micro-wave condition for 5 min, gave a product identical with **3a** (i.e., **3**, R^1=R^2=H) in all respects (m.p., m.m.p., and co-tlc analysis).(**Scheme-I**). Similarly, **3b-3h** compounds have been prepared using MWI of reactants **1a-1h** and **2a-2h** in DMF respectively.

Table-I. Physical data of compounds (3a-h).

Sl. No	Starting compounds.		Product obtained.	MP (^{0}C)	Method-A (Conventional)		Method-B (MW)	
	1	**2**	**3**		Time (hrs)	Yield (min)	Time (min)	Yield (%)
a				212	6	78	10.0	80
b				217	5.5	72	10.0	77
c				248	6.0	77	10.3	79
d				231	6.0	70	10.0	77
e				221	5.0	70	10.2	75
f				247	5.5	68	10.0	73
g				236	5.5	72	10.0	77
h				241	5.0	77	10.3	79



The results of both the reactions are summarized in Table-1. A comparison between the two methods shows that in the microwave technique the reaction time is drastically reduced, and the yields are comparable.

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