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Heterocyclizations via POCl₃-Based Multicomponent Reactions: A New Approach to One-Pot Synthesis of a New Spirosystem, 7-Methyl-5-[4-(aryl/heteryl)thiazol-2-yl]-5,6-diazaspiro[2,4]hept-6-en-4-ones

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HETEROCYCLIZATIONS VIA POCl₃-BASED MULTICOMPONENT REACTIONS: A NEW APPROACH TO ONE-POT SYNTHESIS OF A NEW SPIROSYSTEM, 7-METHYL-5-[4-(ARYL/HETERYL)THIAZOL-2-YL]-5,6-DIAZASPIRO[2,4]HEPT-6-EN-4-ONES

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A novel multicomponent reaction involving phenacylbromide, thiosemicarbazide, and α -acetyl- γ -butyrolactone in the presence of POCl₃, forming 7-methyl-5-[4-(arylheteryl)thiazole-2-yl]-5,6-diaza spiro[2,4]hept-6-en-4-ones in good yields, is described.

Keywords: α -Acetyl- γ -butyrolactone; 3-(2-bromoacetyl)coumarin; phenacylbromides; spiro compound; thiazole

INTRODUCTION

In view of the wide range of biological activates exhibited by 2H-1-benzopyran-2-ones, pyrazoles, and thiazoles, we became interested in synthesizing these moieties in one molecule, which is expected to enhance their biological activity as compared to simple pyrazolothiazoles. Based on these observations, we report the synthesis of a new spiro system, 7-methyl-5-[4-(aryl/heteryl)thiazol-2-yl]-5,6-diazaspiro[2,4]hept-6-en-4-ones.

Thiazoles are generally synthesized by Hantzsch's thiazole synthesis from α -halogenoketones and thioureas or thioamides. Dodson and King^[1] and others^[2] synthesized aminothiazoles by a modification of the method. The method still remains a cumbersome and time-consuming process.

A literature survey^[3] clearly revealed that normally 2-pyrazol-4-yl-substituted thiazoles are prepared in two distinct methods, one involving preparation of thiazole first and then building a pyrazole in the next step or vice versa. Unlike the literature methods, we have synthesized a 2-pyrazol-4-yl-substituted thiazole system in one step.

Though the previous methodologies are quite useful, they have some limitations, such as the requirement to isolate intermediates and longer reaction times, and the overall yields are poor. None of these methods are simple, nor can they be usefully applied for the generation of functionally substituted pyrazolothiazoles. It is thus evident that there remains scope for the development of clean and efficient methodologies involving single-step reactions for the preparation of the title compounds. In the

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present investigation, there is a simultaneous selective ring-closure reaction involving the formation of three rings at time, such as thiazole, pyrazole, and carbocyclic rings, with spiro linkages at the third position of coumarin in an acidic medium.

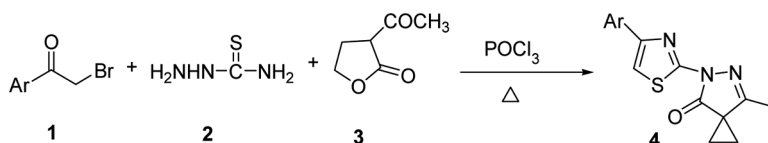
RESULTS AND DISCUSSION

In continuation of our earlier work on the synthesis of heterocyclic systems from α -halo carbonyl compounds,^[4] we report herein a facile, novel route for the synthesis of 7-methyl-5-[4-(aryl/heteryl)-2-yl]-5,6-diazaspiro[2.4]hept-6-en-4-ones in a single step from easily available starting materials. The reaction involves simultaneous cyclization, leading to the formation of thiazole, pyrazolone, and cyclopropane rings. As shown in Scheme 1 and Table 1, the reaction of aryl bromomethylketones/heterylbromomethylketones with thiosemicarbazide and α -bromoacetyl- γ -butyrolactone in POCl₃ under heating yielded the title compounds in one step.

Our experiment was first conducted by adding equimolar quantities of phenacyl bromide, thiosemicarbazide, and α -acetyl- γ -butyrolactone in POCl₃ under heating, which yielded 7-methyl-5-[4-phenyl-thiazol-2-yl]-5,6-diazaspiro[2.4]hept-6-one rather than an expected compound such as {2-[5-hydroxy-4-(2-hydroxy-ethyl)-3-methyl-pyrazol-4-yl]-thiazol-4-yl}benzene, as confirmed by spectral analysis. The infrared (IR) spectra of **4a** displayed bands in the region 1621 cm⁻¹ (amide, -C=O), 1602 cm⁻¹ (-C=N). The ¹H NMR spectrum of **4a** displayed characteristic signals at 1.83 (ABq, 2H, spiro -CH₂-CH₂), 1.94 (ABq, 2H, CH₂-CH₂), and 2.10 (s, 3H, CH₃). In the mass spectrum of **4a**, molecular ion was recorded at *m/z* 306 (M + Na), 284 (M + 1).


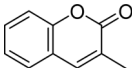
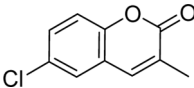
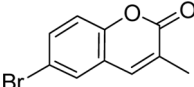
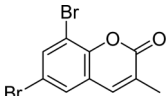
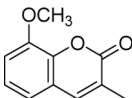
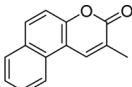
Further examination of the scope of the reaction revealed that substituted 3-(2-bromoacetyl)chromenes, thiosemicarbazide, and α -acetyl- γ -butyrolactone can also participate in the reaction and produce substituted 7-methyl-5-[4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl]-5,6-diazaspiro[2.4]hept-6-en-4-one. The formation of the product (**4b**) was confirmed by spectral and analytical data. For the conformation of this product, we recorded 2D ¹H and ¹³C correlation NMR spectra. In 2D NMR, each spot on the HETCOR plot has been labeled. The carbon peak at 13.1 ppm and the proton singlet at 2.1 ppm correspond to the methyl group, the carbon peaks at 20.2 and 20.2 ppm and the protons of AB quartets at 1.83 and 1.95 ppm correspond to the methylene group, and the carbon peak at 116.7 ppm and the proton singlet at 8.29 ppm correspond to the H-5 of thiazole. The carbon peak at 116.7 ppm and the proton doublet at 7.37 ppm correspond to H-8 of coumarin. The carbon peak at 125.0 ppm and the proton doublet of doublets at 7.28 ppm correspond to the H-6 of coumarin. The carbon peak at 128.8 ppm and the proton doublet at 7.65 ppm correspond to H-5 of coumarin.

The carbon peak at 131.8 ppm and the proton doublet of doublets correspond to the H-7 of coumarin at 7.53 ppm. The carbon peak at 140.1 ppm and the proton



Scheme 1. One-step preparation of 7-methyl-5-[4-aryl/heteryl-thiazol-2-yl]-5,6-diazaspiro[2.4]hept-6-one.

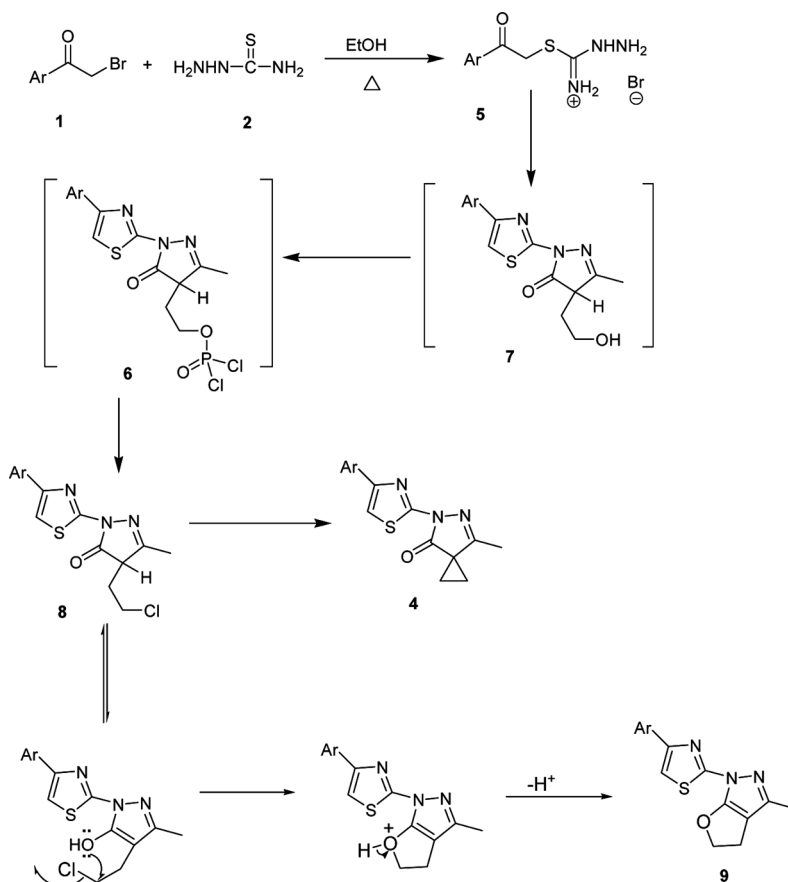
Table 1. Synthesis of 7-methyl-5-[4-phenyl-thiazol-2-yl]-5,6-diazaspiro[2.4]hept-6-one

No.	Ar	Yield ^a (%)	
		Method 1	Method 2
4a		60	45
4b		55	54
4c		60	55
4d		40	48
4e		40	46
4f		55	43
4g		65	45

^aYields refer to isolated yield. Compounds are characterized by ¹H, ¹³C NMR, and IR spectra.

singlet at 8.8 ppm correspond to the H–C₄ of coumarin. The proton of C₄ of coumarin is deshielded. Therefore, a spot on the HETCOR plot for this group appears at 140.1 ppm on the carbon axis and at 8.8 ppm on the proton axis. It is interesting that the methyl group of the diazaspiro[2.4]hept-6-en-4-one appears downfield of the methylene group (2) in the proton spectrum (2.1δ ppm). In the carbon spectrum, however, the carbon peak for methyl appears upfield of methylene carbons. Thus, these HETCOR values confirm the assigned structure. Based on these observations, we concluded that the product was 7-methyl-5-[4-(2-oxo-2*H*-chromen-3-yl)thiazol-2-yl]-5,6-diazaspiro[2.4]hept-6-en-4-one rather than {2-[5-hydroxy-4-(2-hydroxyethyl)-3-methyl-pyrazol-4-yl]-thiazol-4-yl}-chromen-2-one.

Mechanistically, a second possible reaction pathway could be envisaged (Scheme 2) in this process: condensation of aryl/heteryl bromomethylketones with thiosemicarbazide in anhydrous ethanol at room temperature, resulting in the formation of uncyclized 2-oxo-2-(2-aryl/2-oxo-2*H*-chromen-3-yl)ethylhydrazinecarbamidathioatehydrobromide (**5**) (Table 2). Condensation of these uncyclized




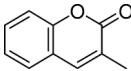
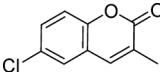
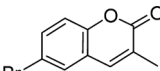
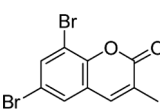

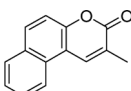
Scheme 2. Method 2: stepwise synthesis of 7-methyl-5-[4-phenyl-thiazol-2-yl]-5,6-diazaspiro[2.4]hept-6-one and mechanism of the reaction.

compounds (5) with α -acetyl- γ -butyrolactone (3) in POCl₃ under reflux resulted in the formation of title compounds (4) instead of the expected 6 or 7 or both (Scheme 2). It is believed that during the reaction of 5 with α -acetyl- γ -butyrolactone in POCl₃, the compound 6 formed changes into the corresponding chloroethyl derivatives 8, which undergo in situ intramolecular cyclization with the loss of HCl to give spiro compound 4. Cyclization of intermediate 7 or 8 leads to either product 4 or 9 or both, depending upon the mode of cyclization. In our case, only one product, 4, was obtained as evidenced by thin-layer chromatography (TLC). The formation 9 can be ruled out on the basis of spectral evidence. It is interesting to note that during the course of the reaction, selective intramolecular ring closure occurs to give 4.

EXPERIMENTAL

All the reagents and solvents were purchased from commercial sources and were used without further purification unless otherwise stated. 3-(2-Bromoacetyl)

Table 2. Synthesis of 2-oxo-2-(phenyl)ethylhydrazine carbimidazo thioatehydrobromide

No.	Ar	Yield ^a (%)
5a		92
5b		92
5c		88
5d		90
5e		88
5f		90
5g		91

^aYields refer to isolated yield. Compounds are characterized by ¹H, ¹³C NMR, and IR spectra.

coumarins^[5] were prepared by the literature procedure. Melting points were determined in open capillaries with a Cintex melting-point apparatus (Mumbai, India) and were uncorrected. CHNS analysis was done on a Carlo Erba EA 1108 automatic elemental analyzer. The purity of the compounds was checked by TLC plates (E. Merck, Mumbai, India). IR spectra (KBr) were recorded on a BrukerWM-4(X) spectrometer (577 model). ¹H NMR spectra were recorded on a Bruker WM-300 spectrometer in δ ppm using tetramethylsilane (TMS) as internal standard. Mass spectra (EI-MS) were determined on a Perkin-Elmer instrument (SCIEX API-2000, ESI) at 12.5 eV.

General Procedure for 4

A mixture of aryl/3-coumarinyl bromomethyl ketone (10 mmol), thiosemicarbazide (10 mmol), and α -acetyl- γ -butyrolactone (10 mmol) in POCl₃ (12 ml) was refluxed for 1 h. The reaction mixture was poured in ice-cold water (60 ml). The product formed was purified by column chromatography on silica (eluent, ethyl acetate/hexanes 1.5:8.5) to give the title compound in 40–65% yield. All the other compounds were prepared by a similar procedure.

7-Methyl-5-[4-phenyl-thiazol-2-yl]-5,6-diazaspiro[2.4]hept-6-one (4a)

Mp 120–122 °C. IR (KBr) ν (cm⁻¹), 1720 (lactone, –C=O), 1621 (amide, –C=O), 1602 (–C=N). ¹H NMR spectrum (300 MHz, CDCl₃) δ ppm: 1.83 (ABq, 2H, spiro –CH₂–CH₂), 1.94 (ABq, 2H, CH₂–CH₂), 2.10 (s, 3H, CH₃), 7.2–7.45 (m, 4H, Ar-H), 7.97 (d, J = 7.8 Hz, 2H, Ar-H); ¹³C NMR spectrum (300 MHz, CDCl₃), 13.06, 20.0 (for two carbons), 33.7, 108.1, 126.9 (for two carbons), 128.5, 128.9 (for two carbons), 134.5, 151.4, 155.9, 162.8, 172.1. ESI-MS: m/z 306 (M⁺ + Na), 284 (M⁺ + 1). Anal. calcd. for C₁₅H₁₃N₃OS: C, 63.58; H, 4.62; N, 14.83; S, 11.32. Found: C, 63.52; H, 4.53; N, 14.79; S, 11.36.

7-Methyl-5-[4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl]-5,6-diazaspiro[2.4]hept-6-en-4-one (4b)

Crystalline solid. 55% yield, mp 270–271 °C. IR (KBr) ν (cm⁻¹), 1720 (lactone, –C=O), 1635 (amide, –C=O), 1610 (–C=N–). ¹H NMR spectrum (300 MHz, CDCl₃) δ ppm: 1.83 (ABq, 2H, spiro CH₂–CH₂), 1.95 (ABq, 2H, spiro CH₂–CH₂), 2.11 (s, 3H, CH₃), 7.37 (d, J = 8.1 Hz, 1H, C₈ of coumarin), 7.28 (dd, J = 8.1 Hz, 1H, C₆ of coumarin), 7.65 (d, J = 7.8 Hz, 1H, C₅ of coumarin), 7.53 (dd, J = 7.8 Hz, 1H, C₇ of coumarin), 8.29 (s, 1H, thiazole), 8.8 (s, 1H, C₄ of coumarin); ¹³C NMR spectrum (300 MHz, CDCl₃): 13.1, 20.2 (for two carbon atoms), 33.8, 115.5, 116.7, 119.9, 120.9, 125, 128.8, 131.8, 140.1, 144.1, 153.4, 155.5, 160.2, 163.2, 172.2. ESI-MS: m/z 352 (M⁺ + 1). Anal. calcd. for C₁₈H₁₃N₃O₃S: C, 61.53; H, 3.73; N, 11.96; S, 9.12. Found: C, 61.59; H, 3.67; N, 11.91; S, 9.08.

5-[4-(6-Chloro-2-oxo-2H-chromen-3-yl)thiazol-2-yl]-7-methyl-5,6-diazaspiro[2.4]hept-6-en-4-one (4c)

Crystalline solid, yield 60%, mp 253–255 °C. IR (KBr), ν (cm⁻¹), 1721 (lactone, –C=O), 1635 (amide, –C=O), 1604 (–C=N). ¹H NMR spectrum (300 MHz, CDCl₃), δ ppm: 1.83 (ABq, 2H, spiro CH₂–CH₂), 1.93 (ABq, 2H, spiro CH₂–CH₂), 2.11 (s, 3H, C₇ methyl of spiro system), 7.30–7.61 (m, 3H, Ar-H), 8.31 (s, 1H, C₅ of thiazole), 8.73 (s, 1H, C₄ of coumarin). ¹³C NMR spectrum (300 MHz, CDCl₃): 13.1, 20.3 (for two carbon atoms), 33.8, 116.3, 118.2, 121.0, 121.9, 127.8, 130.3, 131.7, 138.7, 143.7, 151.8, 155.6, 159.6, 163.3, 172.1. Anal. calcd. for C₁₈H₁₂ClN₃O₃S: C, 56.03; H, 3.13; N, 10.89; S, 8.31. Found: C, 56.11; H, 3.17; N, 10.82; S, 8.34.

5-[4-(6-Bromo-2-oxo-2H-chromen-3-yl)thiazol-2-yl]-7-methyl-5,6-diazaspiro[2.4]hept-6-en-4-one (4d)

Crystalline solid, yield 40%, mp 237–240 °C. IR (KBr), ν (cm⁻¹), 1720 (lactone, –C=O), 1635 (amide, –C=O), 1601 (–C=N). ¹H NMR spectrum (300 MHz, CDCl₃), δ ppm: 1.77 (ABq, 2H, spiro CH₂–CH₂), 2.09 (ABq, 2H, spiro CH₂–CH₂), 2.37 (s, 3H), 7.42 (d, J = 8.4 Hz, 1H, Ar-H), 7.76–7.89 (m, 2H, Ar-H), 8.28 (s, 1H, thiazole), 8.72 (s, 1H, C₄ of coumarin). ESI-MS: m/z 430 (M⁺ + 1). Anal. calcd. for C₁₈H₁₂BrN₃O₃S: C, 50.25; H, 2.81; N, 9.77; S, 7.45. Found: C, 50.17; H, 2.77; N, 9.83; S, 7.41.

5-[4-(6,8-Dibromo-2-oxo-2H-chromen-3-yl)thiazol-2-yl]-7-methyl-5,6-diazaspiro[2.4]hept-6-en-4-one (4e)

Crystalline solid, yield 40%, mp 240–243 °C. IR (KBr), ν (cm⁻¹), 1732 (lactone, –C=O), 1635 (amide, –C=O), 1615 (–C=N). ¹H NMR spectrum (300 MHz, CDCl₃), δ ppm: 1.85 (ABq, 2H, spiro CH₂–CH₂), 1.95 (ABq, 2H, spiro CH₂–CH₂), 2.11 (s, 3H, C₇ methyl of spiro system), 7.68 (m, 1H, Ar-H), 7.92 (s, 1H, aromatic), 8.32 (s, 1H, C₅ thiazole), 8.68 (s, 1H, C₄ of coumarin). Anal. calcd. for C₁₈H₁₁Br₂N₃O₃S: C, 42.46; H, 2.81; N, 8.25; S, 6.30. Found: C, 42.39; H, 2.16; N, 8.21; S, 6.26.

5-[4-(8-Methoxy-2-oxo-2H-chromen-3-yl)thiazol-2-yl]-7-methyl-5,6-diazaspiro[2.4]hept-6-en-4-one (4f)

Crystalline solid, yield 55%, mp 228–230 °C. IR (KBr), ν (cm⁻¹), 1723 (lactone, –C=O), 1625 (amide, –C=O), 1607 (–C=N). ¹H NMR spectrum (300 MHz, CDCl₃), δ ppm: 1.77 (ABq, 2H, spiro CH₂–CH₂), 2.06 (ABq, 2H, spiro CH₂–CH₂), 2.27 (s, 3H, C₇ methyl of spiro system), 3.94 (s, 3H, CH₃ of methoxy group), 7.27–7.53 (m, 3H, Ar-H), 8.19 (s, 1H, C₅ thiazole), 8.69 (s, 1H, C₄ of coumarin). Anal. calcd. for C₁₉H₁₅N₃O₄S: C, 59.83; H, 3.96; N, 11.02; S, 8.41. Found: C, 59.87; H, 3.93; N, 11.10; S, 8.44.

5-[4-(5,6-Benzo-2-oxo-2H-chromen-3-yl)thiazol-2-yl]-7-methyl-5,6-diazaspiro[2.4]hept-6-en-4-one (4g)

Crystalline solid, yield 65%, mp 245–248 °C. IR (KBr), ν (cm⁻¹), 1716 (lactone, –C=O), 1627 (amide, –C=O), 1610 (–C=N). ¹H NMR spectrum (300 MHz, CDCl₃), δ ppm: 1.85 (ABq, 2H, spiro CH₂–CH₂), 1.97 (ABq, 2H, spiro CH₂–CH₂), 2.13 (s, 3H, C₇ methyl of spiro system), 7.50–7.73 (m, 3H, Ar-H), 7.92 (d, J = 8.1 Hz, 1H, aromatic), 7.99 (d, J = 9 Hz, 1H, aromatic), 8.36 (s, 1H, C₅ thiazole), 8.56 (d, J = 6 Hz, 1H, aromatic), 9.55 (s, 1H, C₄ of coumarin). ESI-MS: m/z 402 [M^+ + 1], 421 [M^+ + Na]. Anal. calcd. for C₂₂H₁₅N₃O₃S: C, 65.82; H, 3.77; N, 10.47, S, 7.99. Found: C, 65.87; H, 3.75; N, 10.44; S, 7.96.

General Procedure for Compound 5

A mixture of arylbromomethyl ketone/3-(2-bromoacetyl)chromen-2-one (10 mmol) and thiosemicarbazide (10 mmol) was taken in anhydrous ethanol (25 ml) and stirred for 2 h at 20–25 °C. The crystalline solid thus obtained was filtered and washed with ethanol (5 ml). Compound **5** was isolated in 88–92% yield.

2-Oxo-2-(phenyl)ethylhydrazine Carbimidozothioatehydrobromide (5a)

Yield 92%, mp 205–207 °C. IR (KBr), ν (cm⁻¹), 1607 (br, –C=N), 1660 (–C=O). ¹H NMR (DMSO-*d*₆) δ ppm: 3.61–3.71 (ABq, 2H, SCH₂–), 7.33–7.54 (m, 6H, Ar-H and 1H of –NH, D₂O exchangeable), 7.71 (m, 2H, –NH₂, D₂O exchangeable), 9.39 (s, 1H, –NH, D₂O exchangeable), 10.07 (s, 1H, –C=NH, D₂O exchangeable). ¹³C NMR spectrum (300 MHz, DMSO-*d*₆) δ ppm: 41.4, 97.1,

127.2 (for two carbons), 129.6 (for two carbons), 130, 139.5, 171.2. ESI-MS: m/z 210 ($M^+ + 1$). Anal. calcd. for C₉H₁₁N₃OS · HBr: C, 37.25; H, 4.17; N, 14.48; S, 11.05. Found: C, 37.16; H, 4.09; N, 14.39; S, 11.08.

2-Oxo-2-(2-oxo-2H-chromen-3-yl)ethylhydrazinecarbimidothioate Hydrobromide (5b)

Yield 92%, mp 218–220 °C. IR (KBr), ν (cm⁻¹) 1607 (C=C), 1625 (–C=N), 1654 (–C=O), 1711 (lactone, –C=O). ¹H NMR spectrum (DMSO-*d*₆) δ ppm: 3.40 (d, J = 12 Hz, 1H, SCH₂–), 3.97 (d, J = 12 Hz, 1H, SCH₂–), 5.14 (s, 2H, –NH₂, D₂O exchangeable), 7.37–7.49 (m, 2H, Ar-H), 7.62 (m, 1H, Ar-H), 7.83 (d, J = 7.2 Hz, 1H, Ar-H), 8.09 (s, 1H, –NH, D₂O exchangeable), 8.41 (s, 1H, C₄ of coumarin), 9.17 (s, 1H, –C=NH, D₂O exchangeable), 9.75 (s, 1H, C=NH₂⁺, D₂O exchangeable). ESI-MS: m/z 278 ($M^+ + 1$). Anal. calcd. for C₁₂H₁₁N₃O₃S · HBr: C, 40.24; H, 3.38; N, 11.73; S, 8.95. Found: C, 40.47; H, 3.04; N, 11.67; S, 8.89.

2-Oxo-2-(6-chloro-2-oxo-2H-chromen-3-yl)ethylhydrazinecarbimidothioate Hydrobromide (5c)

Yield 88%, mp 205–207 °C. IR (KBr), ν (cm⁻¹) 1593 (C=C), 1625 (–C=N), 1651 (ketone –C=O), 1712 (lactone–C=O). ¹H NMR spectrum (DMSO-*d*₆) δ ppm: 3.39 (d, J = 12 Hz, 1H, SCH₂–), 3.97 (d, J = 12 Hz, 1H, SCH₂–), 5.14 (s, 2H, –NH₂, D₂O exchangeable), 7.52 (d, J = 9 Hz, 1H, Ar-H), 7.73 (dd, 1H, Ar-H), 8.09–8.16 (m, 2H, aromatic and –NH, D₂O exchangeable), 8.39 (s, 1H, C₄ of coumarin), 9.17 (s, 1H, –C=NH, D₂O exchangeable), 9.77 (s, 1H, C=NH₂⁺, exchangeable). ESI-MS: m/z 312 ($M^+ + 1$). Anal. calcd. for C₁₂H₁₀ClN₃O₃S · HBr: C, 36.72; H, 2.82; N, 9.03; S, 8.16. Found: C, 36.75; H, 2.84; N, 9.01; S, 8.11.

2-Oxo-2-(6-bromo-2-oxo-2H-chromen-3-yl)ethylhydrazinecarbimidothioate Hydrobromide (5d)

Yield 90%, mp 210–212 °C. IR (KBr), ν (cm⁻¹) 1594 (C=C), 1622 (–C=N), 1654 (–C=O), 1713 (lactone–C=O). ¹H NMR spectrum (DMSO-*d*₆) δ ppm: 3.42 (d, J = 15 Hz, 1H, SCH₂–), 3.97 (d, J = 12 Hz, 1H, SCH₂–), 5.14 (s, 2H, –NH₂, D₂O exchangeable), 7.47 (d, J = 9 Hz, 1H, Ar-H), 7.85 (d, J = 9 Hz, 1H, Ar-H), 8.14 (s, 1H, –NH, D₂O exchangeable), 8.23 (s, 1H, Ar-H), 8.38 (s, 1H, C₄ of coumarin), 9.18 (s, 1H, –C=NH, D₂O exchangeable), 9.75 (s, 1H, C=NH₂⁺, exchangeable). ¹³C NMR spectrum (DMSO-*d*₆) δ ppm: 37.4, 93.7, 117.0, 119.1, 121.4, 127.0, 132.2, 135.9, 143.1, 153.6, 159.0, 170.4. Anal. calcd. for C₁₂H₁₀BrN₃O₃S · HBr: C, 32.97; H, 2.54; N, 9.61; S, 7.33. Found: C, 32.91; H, 2.49; N, 9.67; S, 7.39.

2-Oxo-2-(6,8-dibromo-2-oxo-2H-chromen-3-yl)ethylhydrazinecarbimidothioate Hydrobromide (5e)

Yield 88%, mp 210–212 °C. IR (KBr), ν (cm⁻¹) 1603 (C=C), 1627 (–C=N), 1660 (–C=O), 1727 (lactone–C=O). ¹H NMR spectrum (DMSO-*d*₆) δ ppm: 3.38 (d, J = 12 Hz, 1H, SCH₂–), 3.99 (d, J = 12 Hz, 1H, SCH₂–), 5.15 (s, 2H, –NH₂, D₂O exchangeable), 8.19 (s, 1H, –NH, D₂O exchangeable), 8.23 (d, J = 3 Hz, 1H,

Ar-H), 8.26 (d, $J = 3$ Hz, 1H, Ar-H), 8.37 (s, 1H, C₄ of coumarin), 9.21 (s, 1H, $-\text{C}=\text{NH}$, D₂O exchangeable), 9.79 (s, 1H, $\text{C}=\text{NH}_2^+$, exchangeable). Anal. calcd. for C₁₂H₉Br₂N₃O₃S · HBr: C, 27.93; H, 1.95; N, 8.14; S, 6.21. Found: C, 27.88; H, 1.93; N, 8.14; S, 6.21.

2-Oxo-2-(8-methoxy-2-oxo-2H-chromen-3-yl)ethylhydrazinecarbimidothioate Hydrobromide (5f)

Yield 90%, mp 228–230 °C. IR (KBr), ν (cm⁻¹) 1611 (C=C), 1623 ($-\text{C}=\text{N}$), 1656 (ketone $-\text{C}=\text{O}$), 1714 (lactone $-\text{C}=\text{O}$). ¹H NMR spectrum (DMSO-*d*₆) δ ppm: 3.37 (d, $J = 12$ Hz, 1H, SCH₂-), 3.93 (s, 3H, methoxy group), 3.97 (d, $J = 12$ Hz, 1H, SCH₂-), 5.13 (s, 2H, $-\text{NH}_2$, D₂O exchangeable), 7.29–7.46 (m, 3H, Ar-H), 8.08 (s, 1H, $-\text{NH}$, D₂O exchangeable), 8.37 (s, 1H, C₄ of coumarin), 9.17 (s, 1H, $-\text{C}=\text{NH}$, D₂O exchangeable), 9.74 (s, 1H, $\text{C}=\text{NH}_2^+$, exchangeable). Anal. calcd. for C₁₃H₁₃N₃O₃S · HBr: C, 40.22; H, 3.53; N, 10.82; S, 8.26. Found: C, 40.12; H, 3.57; N, 10.77; S, 8.21.

2-Oxo-2-(5,6-benzo-2-oxo-2H-chromen-3-yl)ethylhydrazinecarbimidothioate Hydrobromide (5g)

Yield 91%, mp 240–242 °C. IR (KBr), ν (cm⁻¹) 1606 ($-\text{C}=\text{N}$), 1659 (ketone $-\text{C}=\text{O}$), 1704 (lactone $-\text{C}=\text{O}$), 3345 ($-\text{NH}$). ¹H NMR spectrum (DMSO-*d*₆) δ ppm: 3.46 (d, $J = 12$ Hz, 1H, SCH₂-), 4.06 (d, $J = 12$ Hz, 1H, SCH₂-), 5.20 (s, 2H, $-\text{NH}_2$, D₂O exchangeable), 7.65–7.84 (m, 3H, Ar-H), 8.12 (d, $J = 9$ Hz, 1H, Ar-H), 8.23 (s, 1H, $-\text{NH}$, D₂O exchangeable), 8.31 (d, $J = 9$ Hz, 1H, Ar-H), 8.51 (d, $J = 9$ Hz, 1H, Ar-H), 9.10 (s, 1H, C₄ of coumarin), 9.22 (s, 1H, $-\text{C}=\text{NH}$, D₂O exchangeable), 9.80 (s, 1H, $\text{C}=\text{NH}_2^+$, exchangeable). Anal. calcd. for C₁₆H₁₃N₃O₃S · HBr: C, 47.07; H, 3.46; N, 10.29; S, 7.85. Found: C, 47.01; H, 3.49; N, 10.25; S, 7.81.

General Procedure for Cyclization of 5 with POCl₃, Leading to 4

2-Acetylbutyrolactone (5 mmol) was added to a suspension of 2-oxo-2-(aryl-2-oxo-2H-chromen-3-yl)ethylhydrazinecarbimidothioate hydrobromide 5 (5 mmol) in POCl₃ (7.2 ml) at 20–25 °C. The suspension was heated to 95 °C, and the stirring continued for 2 h. The reaction mixture was cooled to 20 °C, and anhydrous ethanol was added (20 ml). The product was filtered and purified by chromatography on silica gel (eluent, ethyl acetate/hexane 1.5:8.5) to give 4 in 40–50% yield. The compounds obtained by method 2 were found to be identical to those obtained by method 1. This was confirmed by their mixed mp measurements, co-TLC, and spectral data.

CONCLUSION

In summary, we have described an elegant and simple methodology for the synthesis of 7-methyl-5-[4-(aryl/2-oxo-2H-chromen-3-yl)thiazol-2-yl]-5,6-diazaspiro[2.4]hept-6-en-4-one. The synthesis involves a one-step selective ring closure leading to simultaneous formation of three rings at a time. Advantages of the present protocol are (i) ready availability of the starting materials and mild reaction

conditions, (ii) environmentally safe, (iii) simple operational procedure, and (iv) good yields. The protocol is certainly superior to classical methods available for the preparation individual cyclic systems and other multistep syntheses. This reaction can be extended to other heterocyclic α -halo ketones.

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REFERENCES

1. Dodson, R. M.; King, L. C. The reaction of ketones with halogens and thiourea. *J. Am. Chem. Soc.* **1945**, *67*, 2242–2243; (b) King, L. C.; Hlavacek, R. J. The reaction of ketones with iodine and thiourea. *J. Am. Chem. Soc.* **1950**, *72*, 3722–3725.
2. Vardhan, V. A.; Rajeswar Rao, V. Photoalogenation of 3-acetylcoumarins: Facile synthesis of 3-(2-amino-4-thiazolyl)coumarins and their conversion into 3-(2,5-dimethylpyrrol-1-yl)thiazol-4-yl)coumarins. *Ind. J. Chem.* **1997**, *36B*, 1085.
3. Harode, R.; Sharma, T. C. Synthesis of 2-(3-methylpyrazol-5-one-1-yl)-4-ylthiazoles. *J. Indian Chem. Soc.* **1989**, *66*, 282–284.
4. Srimanth, K.; Rajeswar Rao, V.; Krishna, D. R. Synthesis and evaluation of anticancer activity of some imidazothiazolyl, imidazobenzothiazolyl, and dihydroimidazothiazolyl coumarins. *Arzneim. Forsch. Drug Res.* **2002**, *52*(5), 388–392; (b) Rajeswar Rao, V.; Srimanth, V. A facile one-step synthesis of 3-[2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-4-thiazolyl]-2*H*-1-benzopyran-2-ones under solvent-free conditions. *J. Chem. Res.* **2002**, *5*, 420–421; (c) Rajeswar Rao, V.; Vijaya Kumar, P. Facile one-pot synthesis of 3-{2-[5-hydroxy-4-(2-hydroxy-ethyl)-3-methyl-pyrazol-1-yl]-thiazol-4-yl}-chromen-2-ones via a three-component reaction. *Synth. Commun.* **2006**, *36*, 2157–2161; (d) Rajeswar Rao, V.; Seethalakshmi, T.; Vijaya Kumar, P.; Kallianman, P. *N*-[4-(2-Oxo-2*H*-chromen-3-yl)-3-phenyl-3*H*-thiazol-2-ylidene]anilinium bromide methanol solvate. *Acta Cryst. E* **2006**, *E62*, 3771–3773; (e) Rajeswar Rao, V.; Guravaiah, N. A facile one-pot synthesis of 2-pyrazolyl-4-aryl-thiazoles in a three-component reaction. *J. Chem. Res.* **2008**, *4*, 195.
5. Koelsch, C. F. Bromination of 3-acetocoumarin. *J. Am. Chem. Soc.* **1950**, *72*, 2993–2995.