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One Pot, Multi-component Synthesis of 3-[(4-Aryl-thiazol-2-yl)-hydrazono]-1,3-dihydro-indole-2-one

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Abstract A series of 3-[(4-phenyl-thiazol-2-yl)-hydrazono]-1,3-dihydro-indole-2-one(**4**a—**4**g) and 3-{[4-(2-oxo-2*H*-chromen-3-yl)-thiazol-2-yl]-hydrazono}-1,3-dihydro-indol-2-one(**6**a—**6**d) has been prepared in a one-step procedure from condensation reaction of isatin(**1**), thiosemicarbazide(**2**) and bromoacetophenones(**3**)/or 3-(2-bromoacetyl)coumarins(**4**). The method provides a simple and efficient route to prepare the compounds in good yields and in a short experimental time as compared to its stepwise procedure.

Keywords Isatin; Thiazole; Coumarin; Multi-component reaction; One-pot synthesis

1 Introduction

Present challenge for a synthetic chemist is the development of practically simple and efficient organic transformations that allow the rapid creation of molecular complexity and diversity. This has urged the chemists to develop many novel concepts and methodologies. In this viewpoint, multi-component reaction(MCR) has begun presenting real solutions[1—3]. Many novel MCRs have been added to the existing methodologies and successfully applied to all the fields of organic chemistry[4—7]. Such reactions proceed in a single step, thus avoiding the complicated purification operations and allowing the savings of both solvent and reagent, resulting in substantial minimization of waste, labor, time and cost, and often significantly enhancing the overall yields compared to conventional linear syntheses[8,9].

1*H*-Indol-2,3-dione(Isatin) is an endogenous heterocyclic compound found in human beings and animals as biological regulator in the brain, peripheral tissues, and other body fluids[10]. It displays a wide range of biological as well as pharmacological functions[11,12]. Schiff bases and Mannich bases of isatin have a wide range of application in medicine due to their pharmacological properties such as anti-HIV[13], anti-tubercular[14], anti-plasmodical[15], anticonvulsant[16], antifungal[17], anticancer activities[18]. They are also used as insecticide[19] and sedative-hypnotic agents[20]. The isatin moiety can also act as the inhibitor of apoptosis and show antiviral and antibacterial activities when present in a certain compound[21]. Isatin is a versatile substrate used to synthesize a large variety of heterocyclic compounds, such as indoles, quinolines, and it is also a raw material for drug synthesis[22]. It has also been used in a colorimetric screening test for human serum hyperprolinanemia[23], in a colorimetric assay of HIV-1 proteinase[24] and for the estimation of the age of bones in crime investigation[25].

It has been noticed over the years that interesting biological activities[26,27] are associated with thiazole derivatives. A review[28] also shows that coumarins have diverse structural features and versatile biological properties such as anti-microbial, anti-cancer, anti-inflammatory and anti-HIV activities. Tri-heterocyclic thiazoles containing coumarin have *in-vivo* analgesic and anti-inflammatory activities. These compounds were also found to provide significant protection against acetic acid writhing in animal models[29].

The importance of both isatin Schiff's base and phenyl or coumarinyl-thiazole moieties makes it desirable to develop simple and efficient methods to generate new structures constituting a variety of substituents. In line with our ongoing research program in the synthesis of heterocyclic compounds containing sulfur and nitrogen, herein described a one-pot procedure for synthesizing some new, 3-[(4-aryl-thiazol-2-yl)-hydrazono]-1,3-dihydro-indole-2-ones in good yields.

2 Experimental

2.1 Reagents and Apparatuses

3-(2-Bromoacetyl)coumarin derivatives were prepared by literature procedure[30]. All the other reagents and solvents were pure, which were purchased from commercial sources and were used without further purification unless otherwise stated.

Melting points were determined in open capillaries with a Stuart SMP-30 melting point apparatus and were uncorrected. C, H, N, S analyses were done by a Carlo Erba EA 1108 automatic elemental analyzer. The purity of the compounds was checked by thin-layer chromatography(TLC) plates(E. Merck Mumbai, India). Infrared(IR) spectra(KBr) were recorded on a Bruker WM-4(X) spectrometer(577 models). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker WM-400 spectrometer at 400 MHz(^{1}H NMR) and 100 MHz(^{13}C NMR) in DMSO with tetramethylsilane(TMS) as the internal standard and DMSO-d_6 as the solvent. Mass spectra(MS) were determined on a Perkin Elmer mass spectrometer(SCIEX API-2000,

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ESI) at 12.5 eV.

2.2 General Procedure for the Synthesis of 3-[4-Aryl-thiazol-2-yl)-hydrazono]-1,3-dihydro-indole-2-ones(4a—4g, 6a—6d)

1*H*-Indol-2,3-dione(1 mmol), thiosemicarbazide(1 mmol) and phenacylbromide derivative or 3-(2-bromoacetyl)coumarin (1 mmol) were taken in 10 mL of absolute ethanol. To this mixture were added 0.10—0.15 mL of acetic acid that was stirred for about 3—6 h under reflux condition. After completion of the reaction(checked with TLC), the reaction mixture was cooled to room temperature. The product obtained was filtered, washed with alcohol, then with water and recrystallized from suitable solvent.

3-[(4-Phenyl-thiazol-2-yl)-hydrazono]-1,3-dihydro-indol-2-one(**4**a): yield 0.243 g(76%), m. p. 265—267 °C. IR(KBr), $\tilde{\nu}$/cm^{-1}: 3410(N—H, amide), 3191(N—H), 1676(C═O), 1546 (C═N). ^{1}H NMR, δ: 6.97(d, 1H, *J*=7.6 Hz, Ar-H), 7.10(t, 1H, *J*=7.6 Hz, Ar-H), 7.33—7.35(m, 2H, Ar-H), 7.43(t, 2H, *J*=7.6 Hz, Ar-H), 7.55(d, 1H, *J*=7.2 Hz, Ar-H), 7.63(s, 1H, thiazole), 7.90(t, 2H, *J*=4.2 Hz, Ar-H), 11.26(s, 1H, N—H of lactam), 13.35(s, 1H, N—H). ^{13}C NMR(DMSO-d$_6$), δ: 106.71, 111.00, 119.70, 119.78, 122.34, 125.65, 127.90, 128.63, 130.41, 132.02, 133.93, 141.25, 151.02, 163.14, 165.99. MS(ESI), *m/z*: 321.1 (M+1). Elemental anal.(%) calcd. for $C_{17}H_{12}N_4OS$: C 63.73, H 3.78, N 17.49, S 10.01; found: C 63.70, H 3.74, N 17.52, S 10.10.

3-{[4-(4-Chloro-phenyl)-thiazol-2-yl]-hydrazono}-1,3-dihydro-indol-2-one(**4**b): yield 0.243 g(85%), m. p. 287—289 °C. IR, $\tilde{\nu}$/cm^{-1}: 3258(N—H, amide), 3176(N—H), 1690 (C═O), 1544(C═N). ^{1}H NMR, δ: 6.97(d, 1H, *J*=8.0 Hz, Ar-H), 7.08—7.11(m, 1H, Ar-H), 7.33—7.37(m, 1H, Ar-H), 7.47(d, 2H, *J*=1.6 Hz, Ar-H), 7.49—7.55(m, 1H, Ar-H), 7.69(s, 1H, thiazole), 7.92(d, 2H, *J*=8.8 Hz, Ar-H), 11.25(s, 1H, N—H of lactam), 13.35(s, 1H, N—H). ^{13}C NMR(DMSO-d$_6$), δ: 107.47, 111.03, 119.67, 119.83, 122.36, 127.39, 128.64, 130.47, 132.17, 132.37, 132.80, 141.30, 149.77, 163.14, 166.17; MS(ESI), *m/z*: 355.1(M+1). Elemental anal.(%) calcd. for $C_{17}H_{11}ClN_4OS$: C 57.55, H 3.12, N 15.79, S 9.04; found: C 57.51, H 3.16, N 15.74, S 9.92.

3-[(4-*p*-Tolyl-thiazol-2-yl)-hydrazono]-1,3-dihydro-indol-2-one(**4**c): yield 0.264 g(79%), m. p. 276—278 °C. IR, $\tilde{\nu}$/cm^{-1}: 3396(N—H, amide), 3133(N—H), 1686(C═O), 1551(C═N). ^{1}H NMR, δ: 2.33(s, 3H, —CH$_3$ of phenyl), 6.97(d, 1H, *J*=7.6 Hz, Ar-H), 7.09(t, 1H, *J*=7.4 Hz, Ar-H), 7.23(d, 2H, *J*=8.0 Hz, Ar-H), 7.34(t, 1H, *J*=7.8 Hz, Ar-H), 7.54(d, 2H, *J*=7.2 Hz, Ar-H and thiazole proton), 7.78(d, 2H, *J*=8.0 Hz, Ar-H), 11.25(s, 1H, N—H of lactam), 13.34(s, 1H, N—H). Elemental anal.(%) calcd. for $C_{18}H_{14}N_4OS$: C 64.65, H 4.22, N 16.75, S 9.59; found: C 64.61, H 4.25, N 16.78, S 9.55.

3-{[4-(4-Methoxy-phenyl)-thiazol-2-yl]-hydrazono}-1,3-dihydro-indol-2-one(**4**d): yield 0.280 g(80%), m. p. 272—274 °C. IR, $\tilde{\nu}$/cm^{-1}: 3432(N—H, amide), 3198(N—H), 1677 (C═O), 1546(C═N). ^{1}H NMR, δ: 3.79(s, 3H, —OCH$_3$), 6.96—6.99(m, 3H, Ar-H), 7.09(t, 1H, *J*=7.6 Hz, Ar-H), 7.34(t, 1H, *J*=7.8 Hz, Ar-H), 7.46(s, 1H, thiazole), 7.54(d, 1H, *J*=7.2 Hz, Ar-H), 7.83(d, 2H, *J*=8.8 Hz, Ar-H), 11.25(s, 1H, N—H of lactam), 13.34(s, 1H, N—H). ^{13}C NMR(DMSO-d$_6$), δ: 55.12, 104.60, 111.02, 114.01, 114.18, 119.75, 122.34, 126.80, 126.98, 127.04, 130.38, 131.90, 141.23, 159.07, 163.14. Elemental anal.(%) calcd. for $C_{18}H_{14}N_4O_2S$: C 61.70, H 4.03, N 15.99, S 9.15; found: C 61.74, H 4.12, N 15.94, S 9.18.

3-{[4-(4-Nitro-phenyl)-thiazol-2-yl]-hydrazono}-1,3-dihydro-indol-2-one(**4**e): yield 0.290 g(79%), m. p. 296—298 °C. IR, $\tilde{\nu}$/cm^{-1}: 3366(N—H, amide), 3172(N—H), 1691 (C═O), 1549(C═N), 1504, 1338(NO$_2$). ^{1}H NMR, δ: 6.97(d, 1H, *J*=8.0 Hz, Ar-H), 7.09(t, 1H, *J*=7.6 Hz, Ar-H), 7.36(t, 1H, *J*=7.8 Hz, Ar-H), 7.55(d, 1H, *J*=7.6 Hz, Ar-H), 8.01(s, 1H, thiazole), 8.18 (d, 2H, *J*=9.2 Hz, Ar-H), 8.29(t, 2H, *J*=7.2 Hz, Ar-H), 11.27(s, 1H, N—H of lactam), 13.39(s, 1H, N—H). Elemental anal.(%) calcd. for $C_{17}H_{11}N_5O_3S$: C 55.88, H 3.03, N 19.17, S 8.78; found: C 55.83, H 3.12, N 19.21, S 8.82.

3-[(4-Biphenyl-4-yl-thiazol-2-yl)-hydrazono]-1,3-dihydro-indol-2-one(**4**f): yield 0.0317 g(80%), m. p. 310—312 °C. IR, $\tilde{\nu}$/cm^{-1}: 3406(N—H, amide), 3168(N—H), 1686(C═O), 1552 (C═N). ^{1}H NMR, δ: 6.97(d, 1H, *J*=7.6 Hz, Ar-H), 7.10(t, 1H, *J*=7.6 Hz, Ar-H), 7.33—7.40(m, 2H, Ar-H), 7.48(t, 2H, *J*=7.6 Hz, Ar-H), 7.56(d, 1H, *J*=7.6 Hz, Ar-H), 7.70—7.75(m, 5H, Ar-H), 8.00(d, 2H, *J*=8.0 Hz, Ar-H and thiazole proton), 11.29(s, 1H, N—H of lactam), 13.38(s, 1H, N—H). Elemental anal.(%) calcd. for $C_{23}H_{16}N_4OS$: C 69.68, H 4.07, N 14.13, S 8.09; found: C 69.64, H 4.12, N 14.10, S 8.10.

3-{[4-(4-Bromo-phenyl)-thiazol-2-yl]-hydrazono}-1,3-dihydro-indol-2-one(**4**g): yield 0.299 g(75%), m. p. 247—249 °C. IR, $\tilde{\nu}$/cm^{-1}: 3390(N—H, amide), 3129(N—H), 1686 (C═O), 1577(C═N). ^{1}H NMR, δ: 6.97(d, 1H, *J*=7.6 Hz, Ar-H), 7.09(t, 1H, *J*=7.6 Hz, Ar-H), 7.34(t, 1H, *J*=7.8 Hz, Ar-H), 7.61(d, 2H, *J*=8.4 Hz, Ar-H), 7.71(s, 1H, thiazole proton), 7.86(d, 2H, *J*=8.4 Hz, Ar-H), 7.94(d, 1H, *J*=7.2 Hz, Ar-H), 11.25(s, 1H, N—H of lactam), 13.35(s, 1H, N—H). ^{13}C NMR (DMSO-d$_6$), δ: 107.54, 111.01, 119.65, 119.81, 120.96, 122.34, 127.67, 130.46, 131.54, 132.17, 133.12, 141.29, 149.80, 163.12, 166.17. Elemental anal.(%) calcd. for $C_{17}H_{11}BrN_4OS$: C 51.14, H 2.78, N 14.03, S 8.03; found: C 51.18, H 2.63, N 13.98, S 8.10.

3-{[4-(2-Oxo-2*H*-chromen-3-yl)-thiazol-2-yl]-hydrazono}-1,3-dihydro-indol-2-one(**6**a): yield 0.318 g(82%), m. p. 328—330 °C. IR, $\tilde{\nu}$/cm^{-1}: 3451(N—H, amide), 3168(N—H), 1719 (C═O coumarin), 1689(C═O, amide), 1548(C═N). ^{1}H NMR, δ: 6.96(d, 1H, *J*=7.6 Hz, Ar-H), 7.09(t, 1H, *J*=7.8 Hz, Ar-H), 7.37—8.47(m, 3H, Ar-H), 7.54(d, 1H, *J*=7.2 Hz, Ar-H), 7.56(d, 1H, *J*=7.2 Hz, Ar-H), 7.93(d, 1H, *J*=8.0 Hz, Ar-H), 8.00(s, 1H, thiazole proton), 8.76(s, 1H, C4 coumarin), 11.27(s, 1H, N—H lactam), 13.38(s, 1H, N—H). Elemental anal.(%) calcd. for $C_{20}H_{12}N_4O_3S$: C 61.85, H 3.11, N 14.43, S 8.26; found: C 61.81, H 3.15, N 14.47, S 8.30.

3-{[4-(8-Methoxy-2-oxo-2*H*-chromen-3-yl)-thiazol-2-yl]-hydrazono}-1,3-dihydro-indol-2-one(**6**b): yield 0.330 g(79%), m. p. 320—322 °C. IR, $\tilde{\nu}$/cm^{-1}: 3450(N—H, amide), 3292 (N—H), 1712(C═O coumarin), 1686(C═O, amide), 1564 (C═N). ^{1}H NMR, δ: 3.93(s, 3H, —OCH$_3$), 6.96(d, 1H, *J*=7.2 Hz, Ar-H), 7.09(t, 1H, *J*=5.4 Hz, Ar-H), 7.34(t, 3H, *J*=8.6 Hz, Ar-H), 7.46—7.55(m, 2H, Ar-H), 8.00(s, 1H, thiazole proton),

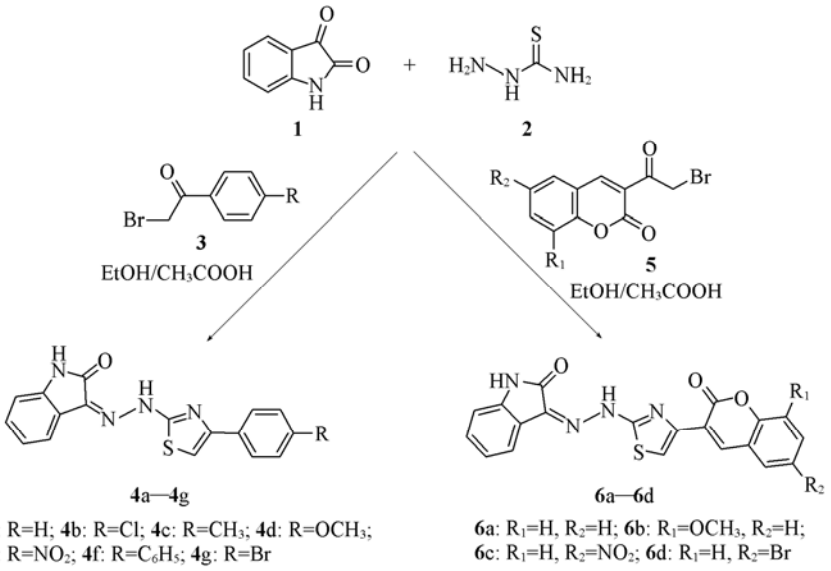
8.72(s, 1H, C_4-coumarin proton), 11.28(s, 1H, N—H of lactam), 13.37(s, 1H, N—H). MS(ESI), *m/z*: 419(M+1). Elemental anal.(%) calcd. for $C_{21}H_{14}N_4O_4S$: C 60.28, H 3.37, N 13.39, S 7.6; found: C 60.32, H 3.32, N 13.42, S 7.64.

3-{[4-(6-Nitro-2-oxo-2*H*-chromen-3-yl)-thiazol-2-yl]-hydrazono}-1,3-dihydro-indol-2-one(**6c**): yield 0.351 g(81%), m. p. 318—320 °C. IR, $\tilde{\nu}$/cm^{-1}: 3448(N—H, amide), 3133 (N—H), 1736(C═O, coumarin), 1694(C═O, amide), 1552 (C═N). ^{1}H NMR, δ: 6.97(d, 1H, *J*=7.6 Hz, Ar-H), 7.09(t, 1H, *J*=7.4 Hz, Ar-H), 7.31—7.35(m, 3H, Ar-H), 7.46—7.48(m, 1H, Ar-H), 7.54(d, 1H, *J*=7.6 Hz, Ar-H), 8.00(s, 1H, thiazole proton), 8.72(s, 1H, C_4-coumarin proton), 11.28(s, 1H, N—H of lactam), 13.37(s, 1H, N—H). Elemental anal.(%) calcd. for $C_{20}H_{11}N_5O_5S$: C 55.43, H 2.56, N 16.16, S 7.40; found: C 55.40, H 2.59, N 16.19, S 7.45.

3-{[4-(6-Bromo-2-oxo-2*H*-chromen-3-yl)-thiazol-2-yl]-hydrazono}-1,3-dihydro-indol-2-one(**6d**): yield 0.363 g(78%), m. p. 333—335 °C. IR, $\tilde{\nu}$/cm^{-1}: 3437(N—H, amide), 3302 (N—H), 1726(C═O, coumarin), 1705(C═O, amide), 1558 (C═N). ^{1}H NMR, δ: 6.97(d, 1H, *J*=8.0 Hz, Ar-H), 7.10(t, 1H, *J*=7.8 Hz, Ar-H), 7.36(t, 1H, *J*=8.4 Hz, Ar-H), 7.43(d, 1H, *J*=8.8 Hz, Ar-H), 7.56(d, 1H, *J*=7.2 Hz, Ar-H), 7.76—8.03(m, 1H, Ar-H), 8.03(s, 1H, thiazole proton), 8.20(d, 1H *J*=2.4 Hz, Ar-H), 8.74(s, 1H, C_4-coumarin proton), 11.28(s, 1H, N—H of lactam), 13.40(s, N—H). MS(ESI), *m/z*: 468(M+1). Elemental anal.(%) calcd. for $C_{20}H_{11}BrN_4O_3S$: C 51.41, H 2.37, N 11.99, S 6.86: found: C 51.45, H 2.32, N 11.93, S 6.82.

3 Results and Discussion

In the earlier work[31,32], a few phenyl derivatives of the title compounds were synthesized *via* a stepwise procedure in which thiosemicarbazone of isatin was first synthesized by the condensation of isatin with thiosemicarbazide. After isolating the intermediate, it was allowed to react with bromoacetophenones in ethanol to give the corresponding products. The above reported method is stepwise linear synthesis. However, in the present work all the reactants *viz*. isatin, thiosemicarbizide and bromoacetophenones/or 3-(2-bromoacetyl)coumarins were added in the same pot with absolute ethanol as a solvent in the presence of catalytic amounts of acetic acid to afford the title compounds(Scheme 1) with reasonably good yields in a less reaction time. Hence, the method avoided the complicated purification operations and allowed the savings of both solvents and reagents.



Scheme 1 Synthesis of 3-[4-aryl-thiazol-2-yl)-hydrazono]-1,3-dihydro-indole-2-one

All the products displayed IR, ^{1}H NMR, and ^{13}C NMR spectra consistent with their assigned structures. For example, the IR spectrum of compound **4**a showed prominent peaks at 3410 and 3191 cm^{-1} for N—H stretching of amide and secondary amino group respectively, 1676 cm^{-1}(lactam C═O), 1546 cm^{-1}(C═N—). The ^{1}H NMR spectrum of compound **4**a showed a singlet peak at δ 7.63 for thiazole proton, two singlet peaks at δ 11.26 and 13.35 for N—H of lactam and N—H of secondary amino group respectively. The peaks of the remaining protons appeared in the usual aromatic region. The ^{13}C NMR spectra also showed peaks for non equivalent carbon atom at δ 106.71, 111.00, 119.70, 119.78, 122.34, 125.65, 127.90, 128.63, 130.41, 132.02, 133.93, 141.25, 151.02, 163.14 and 165.99. The mass spectrum of this compound displayed a quasi-molecular ion peak at 321.1(ESI, M+1 mode).

4 Conclusions

We report herein a one pot efficient method for the synthesis of the title compounds. The reaction involves the formation of both thiazole ring and hydrazonoindole group in one pot operation. The method provides a simple and efficient route to prepare the compounds in good yields and in a short experimental time as compared to the stepwise procedure.

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