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ONE-POT SYNTHESIS OF ARYL(HETARYL)THIAZOLYL-PHTHALAZINE-1,4-DIONES *VIA* MULTICOMPONENT APPROACH

An expeditious one-pot synthesis has been developed to obtain aryl(hetaryl)-substituted thiazolylphthalazine-1,4-diones *via* multicomponent approach. Reaction of phenacyl bromides with thiosemicarbazide and phthalic anhydride afforded arylthiazolylphthalazine-1,4-diones. Reaction of 3-(2-bromoacetyl)coumarins with thiosemicarbazide and phthalic anhydride afforded hetaryl-containing 2-thiazolylphthalazine-1,4-diones under the same reaction conditions in excellent yields. The structures of all the synthesized compounds were confirmed by their analytical and spectral data.

Keywords: 3-(2-bromoacetyl)coumarins, phenacyl bromides, phthalic anhydride, thiosemicarbazide, one-pot reaction.

Multicomponent reactions (MCRs) are those where more than two reactants combine in a sequential manner to give highly selective products that retain majority of the atoms of the starting material [1]. Being one-pot reactions, MCRs generally afford products in good yields and are fundamentally different from two-component reactions [2]. The first documented multicomponent reaction was the Strecker synthesis of α-amino cyanides in 1850 [3]. Later, this MCR strategy has been utilized successfully in Robinson's synthesis of alkaloid tropinone [4] and Hantzsch's synthesis of 1,4-dihydropyridines [5]. The two most important other multicomponent reactions are isocyanide-based Passerini 3-component reaction to produce α-acyloxy carboxamides and the Ugi 4-component reaction [6, 7]. Even though numerous of MCRs have been reported, great efforts are still being made to find and develop new MCRs.

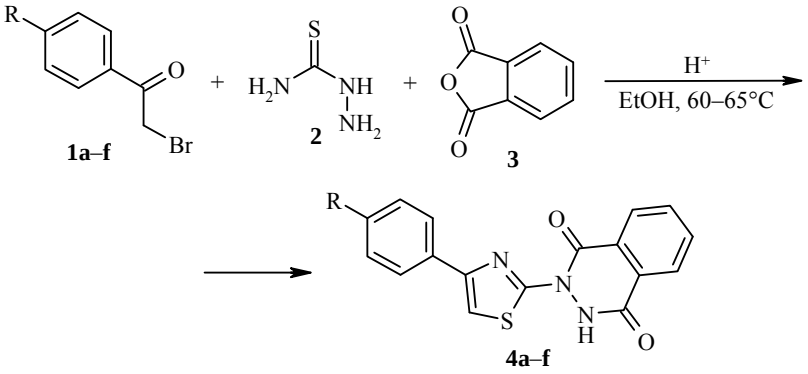
The thiazole ring is an integral part of many potent biologically active molecules such as sulfathiazole (antimicrobial drug), ritonavir (antiretroviral drug), abafungin (antifungal drug), *etc.* [8–10]. On the other hand, 2,3-dihydrophthalazine-1,4-diones are very important class of intermediates in the synthesis of drug molecules such as the antihypertensive agent dihydralazine (1,4-dihydrazinophthalazine) [11]. Moreover, these compounds have attracted considerable attention because they exhibit chemiluminescence [12] and possess pronounced dienophilic properties [13].

On the basis of the above findings and in continuation of our research on the synthesis of novel heterocyclic systems [14–16], we have been interested to synthesize aryl(hetaryl)-containing 2-thiazolylphthalazine-1,4-diones *via* multicomponent approach.

Cardia *et al.* [17] have described a two-step method for the synthesis of above type of compounds. The first step in the synthetic pathway includes the reaction of equimolecular amounts of phthalic anhydrides with thiosemicarbazide in isopropanol in the presence of catalytic amounts of acetic acid. By this method, 2-carbothioamidophthalazines have been prepared. These compounds were then reacted either with α-halo ketones or with α-halo esters to form the corresponding thiazole derivatives.

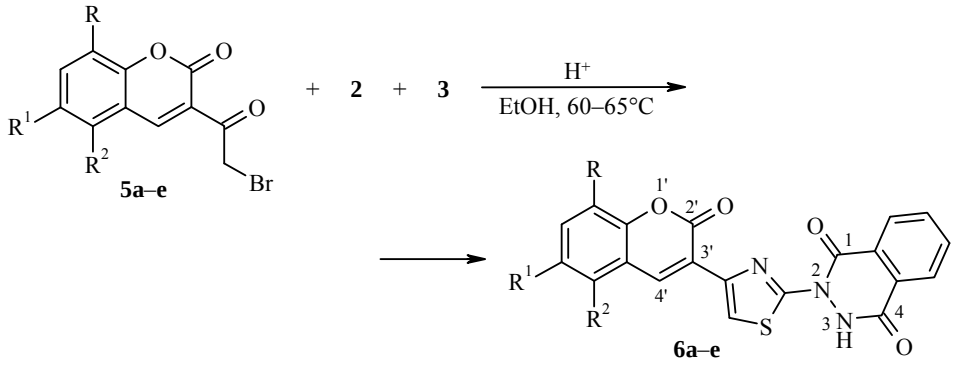
In the present work, a multicomponent approach has been developed for the synthesis of title products using readily available starting materials like 3-(2-bromoacetyl)coumarins, phenacyl bromides, thiosemicarbazide, and phthalic anhydride.

Reaction of various phenacyl bromides **1a–f** with thiosemicarbazide (**2**) and phthalic anhydride (**3**) in acidified ethanolic solution at 60–65°C afforded the corresponding 2-(4-arylthiazol-2-yl)-2,3-dihydrophthalazine-1,4-dione derivatives **4a–f**. The IR spectrum of compound **4a** showed absorption peaks at 1658 and 3428 cm^{-1} which could be assigned to amide carbonyl and NH groups, respectively. The ^1H NMR spectrum of compound **4a** showed a singlet at 2.35 ppm for methyl group and a broad D_2O-exchangeable singlet at 12.49 ppm due to the NH proton, also confirming the structures of the obtained derivatives **4a–f**.



1, **4 a** R = Me, **b** R = OMe, **c** R = Cl, **d** R = Br, **e** R = NO_2, **f** R = Ph

Similarly, the reaction of 3-(2-bromoacetyl)coumarins **5a–e**, thiosemicarbazide (**2**), and phthalic anhydride (**3**) in anhydrous ethanol in the presence of catalytic amounts of acetic acid at 60–65°C afforded the corresponding 2-[4-(2-oxo-2*H*-chromen-3-yl)thiazol-2-yl]-2,3-dihydrophthalazine-1,4-dione derivatives **6a–e** in good yields. The plausible mechanism for the formation of products can be explained by the reaction of thiocarboxamide group of thiosemicarbazide with 3-(2-bromoacetyl)coumarin to give Hantzsch thiazole product with hydrazine moiety at position 2 of thiazole ring. Further reaction with phthalic anhydride gives the corresponding phthalazine-1,4-dione derivative.



5, **6 a** R = R^1 = R^2 = H; **b** R = H, R^1 + R^2 = CH=CH–CH=CH; **c** R = R^2 = H, R^1 = Cl; **d** R = R^1 = Cl, R^2 = H; **e** R = R^1 = Br, R^2 = H

All the structures of the synthesized compounds were confirmed by their analytical and spectral data. The IR spectrum of compound **6a** showed absorption peaks at 1649, 1720, and 3427 cm^{-1}, which correspond to amide carbonyl, lactone carbonyl, and NH groups, respectively. The ^1H NMR spectrum contained the characteristic signal of coumarin H-4' proton at 8.36 ppm. Similarly, ^{13}C NMR spectrum of compound **6a** showed three carbonyl carbons at 158.6, 165.4, and 167.4 ppm. All the above spectral data provide clear evidence for the structures of products **6a**–**e**.

In conclusion, one-pot synthesis of aryl(hetaryl)-substituted thiazolyl-phthalazine-1,4-diones *via* multicomponent approach has been achieved using commercially available starting materials. This method provides some advantages, such as good yields, mild reaction conditions, and easy work-up. The resulting new derivatives may be beneficially utilized in drug research.

EXPERIMENTAL

IR spectra were recorded on a Bruker Tensor 27 spectrophotometer in KBr disks. ^1H and ^{13}C NMR spectra were recorded on a Bruker WM-400 instrument (400 and 100 MHz, respectively) in DMSO-d_6, using TMS as standard. Mass spectra (ESI, 12.5 eV) were determined on Perkin Elmer SCIEX API-2000. Elemental analysis was performed on Carlo Erba EA 1108 automatic elemental analyzer. Melting points were determined in open capillaries with a Cintex melting point apparatus and were uncorrected. The progress of the reactions and purity of the compounds was checked by TLC method using silica gel plates (Merck).

All the reagents and solvents were pure, and purchased from commercial sources, and were used without further purification unless otherwise stated. 3-(2-Bromoacetyl)-coumarins **5a**–**e** were prepared according to literature procedure [18].

Synthesis of compounds 4a–f and 6a–e (General Method). Equimolar mixture of a phenacyl bromide (1 mmol) or a 3-(2-bromoacetyl)coumarin (1 mmol), thiosemicarbazide (91 mg, 1 mmol), and phthalic anhydride (148 mg, 1 mmol) was dissolved in anhydrous EtOH containing catalytic amount of AcOH (12 mg, 0.2 mmol). The reaction mixture was heated at 60–65°C for 2–3 h, and cooled to room temperature. The yellow solid precipitate was filtered, washed with H_2O and recrystallized from EtOH.

2-[4-(4-Methylphenyl)thiazol-2-yl]-2,3-dihydrophthalazine-1,4-dione (4a). Yield 0.251 g, (75%); mp 186–188°C. IR spectrum, ν, cm^{-1}: 3428 (N–H), 1658 (C=O), 1597 (C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.35 (3H, s, CH_3); 7.28 (2H, d, *J* = 8.0, H Ar); 7.85–8.12 (6H, m, H Ar, H-5 Th); 8.40 (1H, d, *J* = 6.8, H Ar); 12.49 (1H, br. s, NH). Mass spectrum, *m/z*: 336 $[M+H]^+$. Found, %: C 64.41; H 3.97; N 12.49. $C_{18}H_{13}N_3O_2S$. Calculated, %: C 64.46; H 3.91; N 12.53.

2-[4-(4-Methoxyphenyl)thiazol-2-yl]-2,3-dihydrophthalazine-1,4-dione (4b). Yield 0.273 g (78%); mp 172–174°C. IR spectrum, ν, cm^{-1}: 3339 (N–H), 1659 (C=O), 1606 (C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.81 (3H, s, OCH_3); 7.04 (2H, d, *J* = 8.8, H Ar); 7.76 (1H, s, H-5 Th); 7.93–8.12 (5H, m, H Ar); 8.40 (1H, d, *J* = 7.6, H Ar); 12.48 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 55.1; 109.9; 114.0; 124.9; 125.1; 127.0; 127.1; 127.3; 127.8; 133.1; 134.4; 149.4; 152.2; 155.9; 156.9; 159.1. Mass spectrum, *m/z*: 352 $[M+H]^+$. Found, %: C 61.50; H 3.68; N 11.91. $C_{18}H_{13}N_3O_3S$. Calculated, %: C 61.53; H 3.73; N 11.96.

2-[4-(4-Chlorophenyl)thiazol-2-yl]-2,3-dihydrophthalazine-1,4-dione (4c). Yield 0.266 g (75%); mp 178–180°C. IR spectrum, ν, cm^{-1}: 3443 (N–H), 1694 (C=O), 1604 (C=N). ^1H NMR spectrum, δ, ppm: 7.36–7.50 (3H, m, H Ar); 7.93–8.13 (6H, m, H Ar, H-5 Th); 12.49 (1H, br. s, NH). Found, %: C 57.31; H 2.78; N 11.78. $C_{17}H_{10}ClN_3O_2S$. Calculated, %: C 57.39; H 2.83; N, 11.81.

2-[4-(4-Bromophenyl)thiazol-2-yl]-2,3-dihydrophthalazine-1,4-dione (4d). Yield 0.288 g (72%); mp 260–262°C. IR spectrum, ν, cm^{-1}: 3331 (NH), 1658 (C=O), 1606 (C=N). ^{1}H NMR spectrum, δ, ppm: 7.67–8.41 (9H, m, H Ar, H-5 Th); 12.54 (1H, br. s, NH). Found, %: C 51.14; H 2.46; N 10.38. $C_{17}H_{10}BrN_3O_2S$. Calculated, %: C 51.01; H 2.52; N 10.50.

2-[4-(4-Nitrophenyl)thiazol-2-yl]-2,3-dihydrophthalazine-1,4-dione (4e). Yield 0.256 g (70%); mp 166–168°C. IR spectrum, ν, cm^{-1}: 3420 (N–H), 1656 (C=O), 1601 (C=N). ^{1}H NMR spectrum, δ, ppm: 7.56–7.86 (5H, m, H Ar, H-5 Th); 8.10–8.29 (4H, m, H Ar); 10.66 (1H, br. s, NH). Found, %: C 55.70; H 2.71; N 15.21. $C_{17}H_{10}N_4O_4S$. Calculated, %: C 55.73; H 2.75; N 15.29.

2-[4-(Biphenyl-4-yl)thiazol-2-yl]-2,3-dihydrophthalazine-1,4-dione (4f). Yield 0.269 g (68%); mp 186–188°C. IR spectrum, ν, cm^{-1}: 3427 (N–H), 1649 (C=O), 1606 (C=N). ^{1}H NMR spectrum, δ, ppm: 7.34–7.96 (14H, m, H Ar, H-5 Th); 10.62 (1H, br. s, NH). Found, %: C 69.46; H 3.74; N 10.50. $C_{23}H_{15}N_3O_2S$. Calculated, %: C 69.50; H 3.80; N 10.57.

2-[4-(2-Oxo-2*H*-chromen-3-yl)thiazol-2-yl]-2,3-dihydrophthalazine-1,4-dione (6a). Yield 0.303 g (78%); mp >300°C. IR spectrum, ν, cm^{-1}: 3427 (N–H), 1720 (C=O lactone), 1649 (C=O amide), 1606 (C=N). ^{1}H NMR spectrum, δ, ppm: 7.33–8.26 (10H, m, H Ar, H-5 Th, NH); 8.36 (1H, s, H-4'). ^{13}C NMR spectrum, δ, ppm: 111.4; 115.8; 115.9; 117.7; 118.9; 120.1; 123.8; 124.6; 127.2; 129.2; 131.7; 133.2; 135.3; 138.5; 139.3; 143.5; 152.2; 158.6; 165.4; 167.4. Mass spectrum, *m/z*: 390 $[M+H]^+$. Found, %: C 61.34; H 2.76; N 10.71. $C_{20}H_{11}N_3O_4S$. Calculated, %: C 61.69; H 2.85; N 10.79.

2-[4-(3-Oxo-3*H*-benzo[*f*]chromen-2-yl)thiazol-2-yl]-2,3-dihydrophthalazine-1,4-dione (6b). Yield 0.324 g (74%); mp >300°C. IR spectrum, ν cm^{-1}: 3423 (N–H), 1739 (C=O lactone), 1687 (C=O amide), 1595 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.65–7.88 (7H, m, H Ar, H-5 Th); 8.11 (2H, d, *J* = 8.0, H Ar); 8.22 (1H, d, *J* = 9.2, H Ar); 8.37 (1H, d, *J* = 8.8, H Ar); 9.33 (1H, s, H-4'); 10.70 (1H, br. s, NH). Mass spectrum, *m/z*: 440 $[M+H]^+$. Found, %: C 65.49; H 2.91; N 9.50. $C_{24}H_{13}N_3O_4S$. Calculated, %: C 65.60; H 2.98; N 9.56.

2-[4-(6-Chloro-2-oxo-2*H*-chromen-3-yl)thiazol-2-yl]-2,3-dihydrophthalazine-1,4-dione (6c). Yield 0.317 g (75%); mp >300°C. IR spectrum, ν, cm^{-1}: 3443 (N–H), 1729 (C=O lactone), 1680 (C=O amide), 1606 (C=N). ^{1}H NMR spectrum, δ, ppm: 7.38–8.27 (8H, m, H Ar, H-5 Th); 8.96 (1H, s, H-4'); 10.44 (1H, br. s, NH). Found, %: C 56.61; H 2.31; N 9.81. $C_{20}H_{10}ClN_3O_4S$. Calculated, %: C 56.68; H 2.38; N 9.91.

2-[4-(6,8-Dichloro-2-oxo-2*H*-chromen-3-yl)thiazol-2-yl]-2,3-dihydrophthalazine-1,4-dione (6d). Yield 0.320 g (70%); mp >300°C. IR spectrum, ν, cm^{-1}: 3425 (N–H), 1731 (C=O lactone), 1685 (C=O amide), 1603 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.48–7.76 (5H, m, H Ar, H-5 Th); 7.85 (1H, d, *J* = 2.8, H Ar); 8.06 (1H, d, *J* = 2.4, H Ar); 8.54 (1H, s, H-4'); 10.68 (1H, br. s, NH). Found, %: C 52.36; H 1.91; N 9.12. $C_{20}H_9Cl_2N_3O_4S$. Calculated, %: C 52.42; H 1.98; N 9.17.

2-[4-(6,8-Dibromo-2-oxo-2*H*-chromen-3-yl)thiazol-2-yl]-2,3-dihydrophthalazine-1,4-dione (6e). Yield 0.426 g (78%); mp 284–286°C. IR spectrum, ν, cm^{-1}: 3435 (N–H), 1743 (C=O lactone), 1688 (C=O amide), 1601 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.56–7.70 (5H, m, H Ar, H-5 Th); 8.13 (1H, d, *J* = 2.0, H Ar); 8.22 (1H, d, *J* = 2.0, H Ar); 8.50 (1H, s, H-4'); 10.69 (1H, br. s, NH). Found, %: C 43.84; H 1.62; N 7.61. $C_{20}H_9Br_2N_3O_4S$. Calculated, %: C 43.90; H 1.66; N 7.68.

R E F E R E N C E S

1. R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown, T. A. Keating, *Acc. Chem. Res.*, **29**, 123 (1996).
2. A. Dömling, I. Ugi, *Angew. Chem., Int. Ed.*, **39**, 3168 (2000).
3. A. Strecker, *Justus Liebigs Ann. Chem.*, **75**, 27 (1850).

4. R. Robinson, *J. Chem. Soc*., **111**, 876 (1917).
5. A. Hantzsch, *Justus Liebigs Ann. Chem*., **215**, 1 (1882).
6. R. Bossio, C. F. Marcos, S. Marcaccini, R. Pepino, *Tetrahedron Lett*., **38**, 2519 (1997).
7. G. F. Ross, E. Herdtweck, I. Ugi, *Tetrahedron*, **58**, 6127 (2002).
8. K. D. Hargrave, F. K. Hess, J. T. Oliver, *J. Med. Chem.*, **26**, 1158 (1983).
9. W. C. Patt, H. W. Hamilton, M. D.Taylor, M. J. Ryan, D. G. Taylor, Jr., C. J. C. Connolly, A. M. Doherty, S. R. Klutchko, I. Sircar, B. A. Steinbaugh, B. L. Batley, C. A. Painchaud, S. T. Rapundalo, B. M. Michniewicz, S. C. J. Olson, *J. Med. Chem.*, **35**, 2562 (1992).
10. F. W. Bell, A. S. Cantrell, M. Högberg, S. R. Jaskunas, N. G. Johansson, C. L. Jordon, M. D. Kinnick, P. Lind, J. M. Morin, Jr., R. Noréen, B. Öberg, J. A. Palkowitz, C. A. Parrish, P. Pranc, C. Sahlberg, R. J. Ternansky, R. T. Vasileff, L. Vrang, S. J. West, H. Zhang, X.-X. Zhou, *J. Med. Chem.*, **38**, 4929 (1995).
11. J. Druey, B. H. Ringier, *Helv. Chim. Acta.*, **34**, 195 (1951).
12. K.-D. Gundermann, H. Fiege, G. Klockenbring, *Justus Liebigs Ann. Chem.*, **738**, 140 (1970).
13. F. Gómez Contreras, M. Lora-Tamayo, A. M. Sanz, *Heterocycles*, **28**, 791 (1989).
14. V. R. Rao, V. R. Reddy, *Khim. Geterotsikl. Soedin*., 465 (2008). [*Chem. Heterocycl. Compd.*, **44**, 360 (2008).]
15. V. S. R. Chunduru, V. R. Rao, *J. Sulfur Chem*., **31**, 545 (2010).
16. V. S. R. Chunduru, V. Rajeswar Rao, *J. Chem. Res*., **34**, 50 (2010).
17. M. C. Cardia, S. Distinto, E. Maccioni, A. Plumitallo, L. Sanna, M. L. Sanna, S. Vigo, *J. Heterocycl. Chem.*, **46**, 674 (2009).
18. V. R. Rao, T. V. P. Rao, *Indian J. Chem.*, **25B**, 413 (1986).

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