Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

Facile one pot multicomponent synthesis of novel 4-(benzofuran-2-yl)-2-(3-(aryl/heteryl)-5-(aryl/heteryl)-4,5-dihydro-1H-pyrazol-1yl)thiazole derivatives

Varun Arandkar, Krishnaiah Vaarla & Rajeswar Rao Vedula

To cite this article: Varun Arandkar, Krishnaiah Vaarla & Rajeswar Rao Vedula (2018) Facile one pot multicomponent synthesis of novel 4-(benzofuran-2-yl)-2-(3-(aryl/heteryl)-5-(aryl/heteryl)-4,5-dihydro-1H-pyrazol-1yl)thiazole derivatives, Synthetic Communications, 48:11, 1285-1290, DOI: 10.1080/00397911.2018.1440600

To link to this article: https://doi.org/10.1080/00397911.2018.1440600

SYNTHETIC COMMUNICATIONS®
2018, VOL. 48, NO. 11, 1285–1290
https://doi.org/10.1080/00397911.2018.1440600

Taylor & Francis
Taylor & Francis Group

Facile one pot multicomponent synthesis of novel 4-(benzofuran-2-yl)-2-(3-(aryl/heteryl)-5-(aryl/heteryl)-4,5-dihydro-1*H*-pyrazol-1yl)thiazole derivatives

Varun Arandkar, Krishnaiah Vaarla, and Rajeswar Rao Vedula

Department of Chemistry, National Institute of Technology, Warangal, Telangana, India

ABSTRACT

An efficient base catalyzed one pot multicomponent reaction of aryl/hetryl chalcones, thiosemicarbazide and 1-(benzofuran-2-yl)-2-bromoethan-1-one was developed to synthesize the novel 4-(benzofuran-2-yl)-2-(3-(aryl/heteryl)-5-(aryl/heteryl)-4,5-dihydro-1*H*-pyrazol-1yl)thiazole derivatives.

GRAPHICAL ABSTRACT

ARTICLE HISTORY
Received 23 December 2017

KEYWORDS
1-(Benzofuran-2-yl)-2-bromoethan-1-one; dihydropyrazolylthiazoles; multicomponent reaction

Introduction

In organic synthesis, target oriented method development has a long history and the academia and industries have been focusing on method development to achieve the desired molecule. The current organic synthetic methods have focused on stereo and regio selective approaches to achieve structural complex molecules with drug-like properties through simple reaction conditions with high efficiency. Multicomponent reactions (MCRs) are among the best synthetic methods to achieve the target molecule libraries and interest in MCRs has surged during recent years. MCRs are organic chemical transformations in which three or more reactants combine to generate a single product in a one pot reaction and in a single operation under mild reaction conditions, in an efficient way with high atom economy. MCRs have several advantages over conventional linear step synthesis.[1] MCRs are widely used for the synthesis of natural products,[2–4] organic materials, polymers,[5–7] and bioactive molecules.[8,9]

Thiazoles are the important organic molecules containing sulfur and nitrogen hetero atoms in a five-membered hetero cyclic system. Thiazoles are widely distributed in natural and synthetic medicines and have wide therapeutic applications[10–16] and that makes them one of the best studied compounds. Some of the thiazoles are available as therapeutic drugs

CONTACT Rajeswar Rao Vedula rajeswarnitw@gmail.com Department of Chemistry, National Institute of Technology, Warangal, Telangana 506004, India.
Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.
Supplemental data for this article can be accessed on the publisher's website.

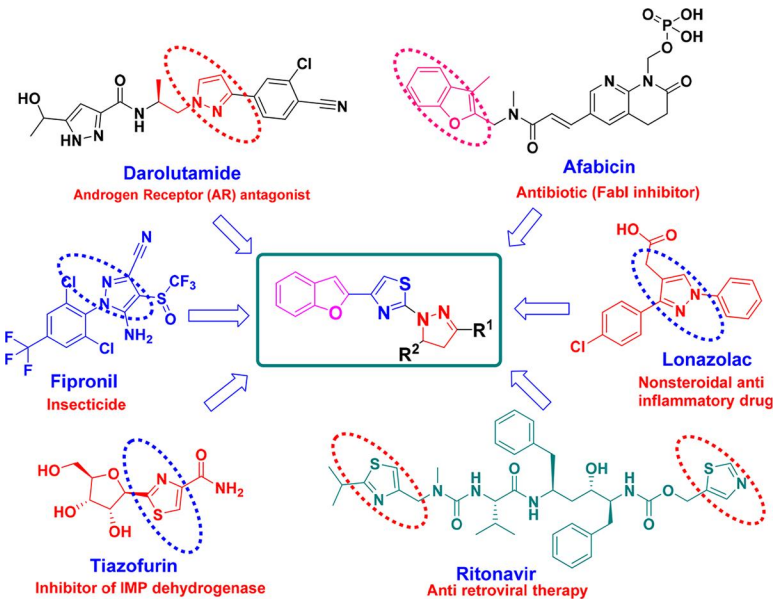


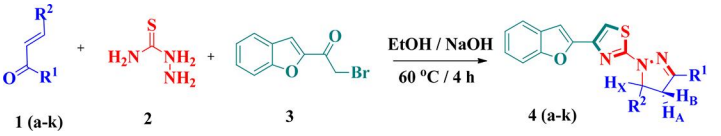
Figure 1. Design strategy adopted for the synthesis of 4,5-dihydro-1H-pyrazol-1yl)thiazole derivatives.

in the market these being antineoplastic (dasatinib, tiazofurin), anti-inflammatory (fentiazac, meloxicam), antiulcer (nizatidine), antifungal (ravuconazole), antiviral (ritonavir), and these thiazoles are also widely used in agriculture (insecticides, fungicides, and herbicides) and material applications. Pyrazoles are also well studied heterocyclic compounds with huge therapeutic value.[17–25] Pyrazoles were found to possess antibacterial, antifungal, antiviral, antitubercular, antitumor, and analgesic activities. Some of the potential therapeutic agents are shown in Figure 1.

In recent years, molecular hybridization technique has been used to generate potential therapeutic molecules. In view of the important applications of these heterocyclic compounds in the field of medicinal and material chemistry, we became interested in an efficient one pot multicomponent approach to synthesize 4-(benzofuran-2-yl)-2-(3-(aryl/heteryl)-5-(aryl/heteryl)-4,5-dihydro-1*H*-pyrazol-1yl)thiazole derivatives under mild reaction conditions with high yields.

Results and discussion

In the present study, the target 4-(benzofuran-2-yl)-2-(3-(aryl/heteryl)-5-(aryl/heteryl)-4,5-dihydro-1*H*-pyrazol-1yl)thiazole derivatives were synthesized using aryl/hetryl chalcones, thiosemicarbazide and 1-(benzofuran-2-yl)-2-bromoethan-1-one as shown in Scheme 1.



Scheme 1. Synthesis of **4a–k**.

Table 1. A model reaction for the synthesis of compound **4e**.

Entry	Solvent	Base	Yield (%)	Reaction time (h)
1		NaOH (0.5 equiv.)	30	12
2		KOH (0.5 equiv.)	38	12
3		NaOH (1.0 equiv.)	46	8
4	Methanol	KOH (1.0 equiv.)	45	8
5		NaOH (1.5 equiv.)	55	6
6		KOH (1.5 equiv.)	54	6
7		NaOH (2.0 equiv.)	55	6
8		KOH (2.0 equiv.)	50	6
9		NaOH (0.5 equiv.)	44	12
10		KOH (0.5 equiv.)	46	12
11		NaOH (1.0 equiv.)	55	8
12	Ethanol	KOH (1.0 equiv.)	48	8
13		**NaOH (1.5 equiv.)**	**93**	**4**
14		KOH (1.5 equiv.)	64	4
15		NaOH (2.0 equiv.)	62	4
16		KOH (2.0 equiv.)	57	4

Bold values indicate the optimized condition to get the compound **4e**.

The starting materials aryl/hetryl chalcones were prepared by the Claisen–Schmidt condensation[26,27] of aryl/hetryl aldehyde with aryl/hetryl ketones using 10% aq. NaOH in ethanol at room temperature, 1-(benzofuran-2-yl)-2-bromoethan-1-one[28] was prepared as per the procedure given in literature using 2-acetyl benzofuran and bromine in presence of chloroform.

In the preliminary study, we performed the reaction of the desired products 4-(benzofuran-2-yl)-2-(3,5-diaryl/heteryl-4,5-dihydro-1*H*-pyrazol-1yl)thiazoles in presence of methanol/ethanol by quantifying the base equivalents as shown in Table 1. Initially we tried the reaction at 60 °C with 0.5 equiv. of NaOH, but the reaction time was high and the yields of the products were poor. In the next trials, the concentration of NaOH was increased to 1.0, 1.5, and 2.0 equiv. and it was observed that the yields increased and the reaction time was minimized. Similarly, the reaction was performed with KOH and the results are shown in Table 1. It was observed that increasing the concentration of base beyond 2.0 equiv. did not increase the yield. After several trials of base concentration modifications, the base concentration (NaOH 1.5 equiv.) was optimized to synthesize the target compounds through a one pot multicomponent approach in short reaction time with good yields as shown in Table 2.

Table 2. Yield of compounds **4a–k**.

S. no.	Compound[a]	R^1	R^2	Yield (%)[b]
1	**4a**	Benzofuran-2-yl	4-Bromophenyl	82
2	**4b**	Benzofuran-2-yl	4-Methoxyphenyl	76
3	**4c**	4-Fluorophenyl	Furan-2-yl	85
4	**4d**	Thiophen-2-yl	4-Chlorophenyl	81
5	**4e**	Thiophen-2-yl	Phenyl	93
6	**4f**	Thiophen-2-yl	3,4,5-Trimethoxyphenyl	88
7	**4g**	Thiophen-2-yl	4-Bromophenyl	82
8	**4h**	Thiophen-2-yl	4-Fluorophenyl	75
9	**4i**	4-Methoxyphenyl	Furan-2-yl	91
10	**4j**	Thiophen-2-yl	*N*,*N*-Dimethylaniline	89
11	**4k**	Thiophen-2-yl	4-Methoxyphenyl	78

[a]Reaction conditions: chalcone (1 equiv.), thiosemicarbazide (1 equiv.), 2-(bromo acetyl) benzofuran (1 equiv.), sodium hydroxide (1.5 equiv.) in ethanol solvent at 60 °C.
[b]Isolated yields.

The newly synthesized compounds were characterized by their physical and analytical data. The proton NMR spectrum of the compounds exhibited characteristic ABX pattern for the three protons present in dihydropyrazole ring at fourth and fifth position and displayed three double doublets (dd). The ^{1}H NMR of compound **4a** showed characteristic peaks at δ 3.38 (dd, $J = 17.6$ Hz, 6.4 Hz, 1H, H_A), 3.97 (dd, $J = 17.2$ Hz, 12 Hz, 1H, H_B), 5.68 (dd, $J = 12$ Hz, 6.8 Hz, 1H, H_X) ppm integrating for one proton each were assigned to H_A, H_B, H_X protons of dihydropyrazole ring while the aromatic protons appeared at δ 6.85–7.62 ppm. In ^{13}C NMR of compound **4a** the methylene carbon and methine carbon atoms of dihydropyrazole appeared at δ 42.99 and 63.87 ppm respectively. The remaining sp^2 hybridized carbons appeared from 102.90 to 154.79 ppm. The most down fielded peak is due to C-2 carbon of thiazole at 164.75 ppm. The mass spectrum for compound **4a** displayed $(M+H)^+$ at 540.25.

Experimental

The reagents used in the present study were purchased from commercial sources and used without any further purification. The progress of the reaction was monitored through thin layer chromatography on silica plate (Merck Kieselgel 60 F_{254} aluminum plates) and visualization of spots was done under UV–Visible light (254 and 356 nm). Melting points were identified using Stuart melting point apparatus (SMP-30). The NMR characterization (^{1}H and ^{13}C) was done using Bruker AV-400 spectrometer. The mass spectral characterization was done using Water Micromass Quattro API technique. CHN analysis was done using Carlo Erba 1108 elemental analyzer.

General procedure for the synthesis of 4-(benzofuran-2-yl)-2-(3,5-diaryl/ heteryl-4,5-dihydro-1H-pyrazol-1yl)thiazole derivatives

A mixture of chalcone (**1a–k**, 1 mmol), thiosemicarbazide (**2**, 1 mmol) and 1-(benzofuran-2-yl)-2-bromoethan-1-one (**3**, 1 mmol) was taken in a round bottom flask. To this 5 mL of ethanol was added and stirred at room temperature for about 10 min. Then the reaction mixture was treated with NaOH (1.5 equiv.) and heated at 60 °C for about 4 h. The progress of the reaction was monitored through thin layer chromatography using ethyl acetate and hexane (1:1) as mobile phase. After completion of the reaction the reaction mixture was cooled to room temperature, solid separated was filtered, washed with ethanol, dried and recrystallized from ethanol.

4-(Benzofuran-2-yl)-2-(3-(benzofuran-2-yl)-5-(4-bromophenyl)-4,5-dihydro-1H pyrazol-1-yl) thiazole (4a)

A mixture of 1-(benzofuran-2-yl)-3-(4-bromophenyl)prop-2-en-1-one (**1a**, 0.327 g, 1 mmol), thiosemicarbazide (**2**, 0.091 g, 1 mmol) and 1-(benzofuran-2-yl)-2-bromoethan-1-one (**3**, 0.239 g, 1 mmol) was taken in a round bottom flask. To this 5 mL of ethanol was added and stirred at room temperature for about 10 min. Then the reaction mixture was treated with NaOH (0.060 g, 1.5 mmol) and heated at 60 °C for about 4.5 h. The progress of the reaction was monitored through thin layer chromatography using ethyl acetate and hexane (1:1) as mobile phase. After completion of the reaction the reaction mixture was cooled to room temperature, solid separated was filtered, washed with ethanol, dried and recrystallized from ethanol. Yellow solid, mp: 256–258 °C, ^{1}H NMR (400 MHz,

$CDCl_3$, ppm): δ 3.38 (dd, $J = 17.6$, 6.4 Hz, 1H, pyrazole-H_A), 3.97 (dd, $J = 17.2$, 12 Hz, 1H, pyrazole-H_B), 5.68 (dd, $J = 12$, 6.8 Hz, 1H, pyrazole-H_X), 6.85 (s, 1H, Ar-H), 7.07 (d, $J = 9.6$ Hz, 2H, Ar-H), 7.18–7.23 (m, 2H, Ar-H), 7.36–7.45 (m, 5H, Ar-H), 7.54–7.62 (m, 5H, Ar-H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 42.99, 63.87, 102.90, 106.44, 108.32, 111.00, 111.76, 121.21, 121.63, 124.28, 125.18, 126.24, 130.05, 130.46, 143.10, 143.22, 143.49, 148.08, 152.22, 154.79, 155.55, 164.75 ppm; MS (ESI *m/z* %): 540.25 $[M+H]^+$; Anal. Calcd. for $C_{28}H_{18}BrN_3O_2S$: C, 62.23; H, 3.36; N, 7.78; S, 5.93%. Found: C, 62.29; H, 3.42; N, 7.73; S, 5.87%.

Conclusion

In summary, we have developed an efficient protocol for simultaneous formation of two potential heterocyclic rings like thiazole and dihydropyrazole derivatives through a multicomponent reaction approach of deferent aryl/hetryl chalcones, thiosemicarbazide and 1-(benzofuran-2-yl)-2-bromoethan-1-one in ethanol in presence of aqueous NaOH in a shorter reaction time.

Acknowledgments

The authors acknowledge the Director, National Institute of Technology-Warangal for providing the research facilities. One of the authors, Varun Arandkar acknowledges University Grants Commission, New Delhi for providing him with research fellowship.

Funding

This work was supported by University Grants Commission-New Delhi: [Grant number F. 2-9/2005 (SA)].

References

[1] Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29* (3), 123–131.
[2] Huang, B.; Zeng, L.; Shen, Y.; Cui, S. *Angew. Chemie Int. Ed.* **2017**, *56* (16), 4565–4568.
[3] Eckert, H. *Molecules* **2017**, *22* (3), 349.
[4] Morejón, M. C.; Laub, A.; Kaluđerović, G. N.; Puentes, A. R.; Hmedat, A. N.; Otero-González, A. J.; Rivera, D. G.; Wessjohann, L. A. *Org. Biomol. Chem.* **2017**, *15* (17), 3628–3637.
[5] Haven, J. J.; Baeten, E.; Claes, J.; Vandenbergh, J.; Junkers, T. *Polym. Chem.* **2017**, *8* (19), 2972–2978.
[6] Zhang, H.-Y.; Hao, X.-P.; Mo, L.-P.; Liu, S.-S.; Zhang, W.-B.; Zhang, Z.-H. *New J. Chem.* **2017**, *41* (15), 7108–7115.
[7] Yaghoubi, A.; Dekamin, M. G.; Arefi, E.; Karimi, B. *J. Colloid Interface Sci.* **2017**, *505*, 956–963.
[8] Slobbe, P.; Ruijter, E.; Orru, R. V. A. *MedChemComm* **2012**, *3* (10), 1189.
[9] Salve, P. S.; Alegaon, S. G.; Sriram, D. *Bioorg. Med. Chem. Lett.* **2017**, *27* (8), 1859–1866.
[10] de Sá, N. P.; de Lima, C. M.; Lino, C. I.; Barbeira, P. J. S.; de Matos Baltazar, L.; Santos, D. A.; de Oliveira, R. B.; Mylonakis, E.; Fuchs, B. B.; Johann, S. *Antimicrob. Agents Chemother.* **2017**, *61* (8), e02700–e02716.
[11] Green, J. P.; Cryer, S. J.; Marafie, J.; White, A. J. P.; Heeney, M. *Organometallics* **2017**, *36* (14), 2632–2636.
[12] Bouherrou, H.; Saidoun, A.; Abderrahmani, A.; Abdellaziz, L.; Rachedi, Y.; Dumas, F.; Demenceau, A. *Molecules* **2017**, *22* (5), 757.
[13] Shaik, S. P.; Nayak, V. L.; Sultana, F.; Rao, A. V. S.; Shaik, A. B.; Babu, K. S.; Kamal, A. *Eur. J. Med. Chem.* **2017**, *126*, 36–51.

[14] Pacca, C. C.; Marques, R. E.; Espindola, J. W. P.; Filho, G. B. O. O.; Leite, A. C. L.; Teixeira, M. M.; Nogueira, M. L. *Biomed. Pharmacother.* **2017**, *87*, 381–387.
[15] Chau, N.-Y.; Ho, P.-Y.; Ho, C.-L.; Ma, D.; Wong, W.-Y. *J. Organomet. Chem.* **2017**, *829* (iii), 92–100.
[16] Da Silva, E. B.; Oliveira e Silva, D. A.; Oliveira, A. R.; da Silva Mendes, C. H.; dos Santos, T. A. R.; da Silva, A. C.; de Castro, M. C. A.; Ferreira, R. S.; Moreira, D. R. M.; Cardoso, M. V. d. O.; *Eur. J. Med. Chem.* **2017**, *130*, 39–50.
[17] Illicachi, L.; Montalvo-Acosta, J.; Insuasty, A.; Quiroga, J.; Abonia, R.; Sortino, M.; Zacchino, S.; Insuasty, B. *Molecules* **2017**, *22* (9), 1476.
[18] Faidallah, H. M.; Rostom, S. A. F. *Arch. Pharm. (Weinheim)* **2017**, *350* (5), 1700025.
[19] Corona, A.; Onnis, V.; Deplano, A.; Bianco, G.; Demurtas, M.; Distinto, S.; Cheng, Y.-C.; Alcaro, S.; Esposito, F.; Tramontano, E. *Pathog. Dis.* **2017**, *75* (6), 1–22.
[20] Nossier, E.; Fahmy, H.; Khalifa, N.; El-Eraky, W.; Baset, M. *Molecules* **2017**, *22* (4), 512.
[21] Xie, Y.; Ruan, X.-H.; Gong, H.-Y.; Wang, Y.-H.; Wang, X.-B.; Zhang, J.-P.; Li, Q.; Xue, W. *J. Heterocycl. Chem.* **2017**, *54* (5), 2644–2649.
[22] Mondal, G.; Jana, H.; Acharjya, M.; Santra, A.; Bera, P.; Jana, A.; Panja, A.; Bera, P. *Med. Chem. Res.* **2017**, *26*(11), 3046–3056.
[23] Ramírez-Prada, J.; Robledo, S. M.; Vélez, I. D.; Crespo, M. d. P.; Quiroga, J.; Abonia, R.; Montoya, A.; Svetaz, L.; Zacchino, S.; Insuasty, B. *Eur. J. Med. Chem.* **2017**, *131*, 237–254.
[24] Chougala, B. M.; Samundeeswari, S.; Holiyachi, M.; Shastri, L. A.; Dodamani, S.; Jalalpure, S.; Dixit, S. R.; Joshi, S. D.; Sunagar, V. A. *Eur. J. Med. Chem.* **2017**, *125*, 101–116.
[25] Jacob, K. S.; Ganguly, S.; Kumar, P.; Poddar, R.; Kumar, A. *J. Biomol. Struct. Dyn.* **2017**, *35* (7), 1446–1463.
[26] Hwang, K.-J.; Kim, H.-S.; Han, I.-C.; Kim, B.-T. *Bull. Korean Chem. Soc.* **2012**, *33* (8), 2585–2591.
[27] Ocak İskeleli, N.; Işık, Ş.; Özdemir, Z.; Bilgin, A. *Acta Crystallogr. Sect. E Struct. Reports Online* **2005**, *61* (5), o1356–o1358.
[28] Dawood, K. M.; Mohamed, H. A.; Abdel-Wahab, B. F. *Chem. Heterocycl. Compd.* **2010**, *46* (2), 131–139.