Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gsrp20

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Published online: 11 Feb 2014.

To cite this article: Mohammad M. Ghanbari, Marzieh Jamali & Gyula Batta , Journal of Sulfur Chemistry (2014): Solvent-free, mild, facile, and rapid one-pot three-component synthesis of some novel imidazo[2,1-b]naphtho[1,2-e][1,3] thiazin-10-ones using p-TSA, Journal of Sulfur Chemistry, DOI: 10.1080/17415993.2014.885031

To link to this article: http://dx.doi.org/10.1080/17415993.2014.885031

Journal of Sulfur Chemistry, 2014
http://dx.doi.org/10.1080/17415993.2014.885031

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Solvent-free, mild, facile, and rapid one-pot three-component synthesis of some novel imidazo[2,1-b]naphtho[1,2-e][1,3] thiazin-10-ones using *p*-TSA

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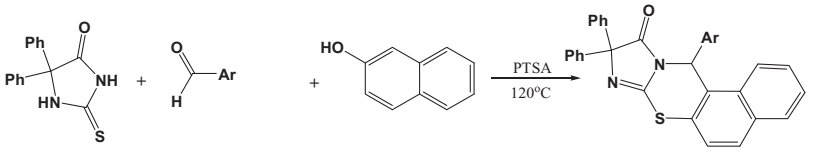
(*Received 3 December 2013; accepted 15 January 2014*)

Novel [2,1-b]naphtho[1,2-e][1,3]thiazin-10-ones were synthesized in 63–89% yield via a three-component reaction of an aromatic aldehyde, β-naphthol, and thiohydantoin in the presence of 10 mol% *p*-toluene sulfonic acid under solvent-free conditions. This is the first protocol to be reported for the synthesis of the title compounds. The significant features of the present protocol are simplicity, high yields, eco-friendliness, and convenient purification that does not require chromatography.



Keywords: thiohydantoins; aldehyde; β-naphthol; one-pot reaction; solvent-free

1. Introduction

Natural and synthetic heterocycles have recently attracted much attention in the fields of agrochemical and medicinal chemistry due to their wide range of biological activities and therapeutic applications.[1–3] Hydantoin and 2-thiohydantoin derivatives are important nitrogen containing heterocycles, which play key roles in the production of amino acids,[4] valuable intermediates for the synthesis of pharmaceuticals and biologically active compounds, such as antibiotics, anti-diabetics, anti-cancer drugs, pesticides, antiarrhythmics, anticonvulsant agents, and other biologically activities.[5–7] As part of our study on heterocyclic and carbocyclic systems,[8–13] we report the synthesis of 9,9-diphenyl-12-aryl-9H-imidazo[2,1-b]naphtho[1,2-e][1,3]thiazin-10(12H)-one, using a green synthetic method (Table 1). This new one-pot synthesis involves the reaction of thiohydantoins **1**, aromatic aldehyde **2** and β-naphthol in the presence of a catalytic amount of *p*-toluene sulfonic acid (TSA) under thermal solvent-free conditions (Scheme 1).

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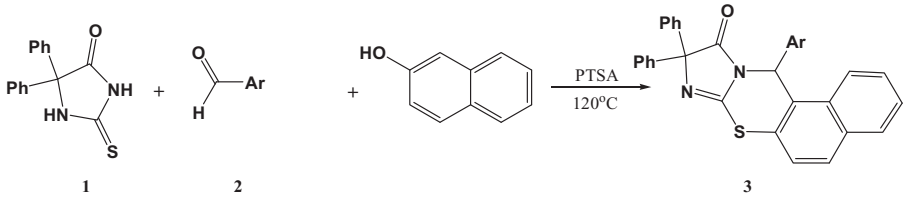
Table 1. Synthesis of 9,9-diphenyl-12-aryl-9H-imidazo[2,1-b] naphtho[1,2-e][1,3]thiazin-10(12H)-one derivatives in the presence of *p*-TSA under solvent-free conditions.

Entry	Ar	Products	Yield (%)	M.p. (°C)
1	4-MeC_6H_4	**3a**	72	203
2	4-ClC_6H_4	**3b**	79	208
3	4-$NO_2C_6H_4$	**3c**	87	328
4	4-$MeOC_6H_4$	**3d**	63	343
5	4-OHC_6H_4	**3e**	84	187
6	2,4-$DiOHC_6H_3$	**3f**	89	Red oil
7	4-FC_6H_4	**3g**	83	213–215
8	5-Br-2-OHC_6H_3	**3h**	69	190–192

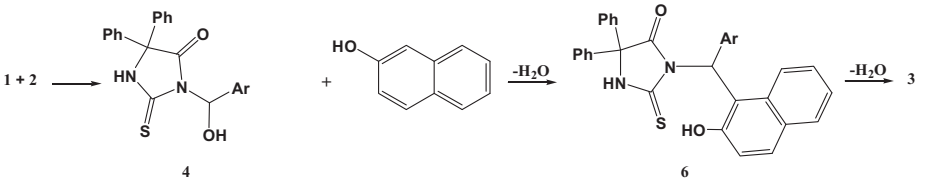


Scheme 1. Synthesis of imidazo [2,1-b]naphtho[1,2-e][1,3]thiazin-10-ones.

2. Results and discussion

In a typical reaction, benzaldehyde (1.0 mmol) was reacted with β-naphthol (1.0 mmol) and thiohydantoin (1.0 mmol) in the presence of a catalytic amount of *p*-TSA under thermal solvent-free conditions to obtain 9,9-diphenyl-12-aryl-9H-imidazo[2,1-b]naphtho[1,2-e][1,3]thiazin-10(12H)-one in good yield. Salient features of this method are mild reaction conditions, eco-friendliness, ease of isolation of product, and an excellent reusability of the catalyst.

Although we have not yet established experimental proof for the mechanism of the formation of compounds **3**, a possible rationalization for the formation of the products is proposed in Scheme 2. It is sensible to assume that the initial event is the formation of intermediates **4** from the arylaldehyde and thiohyantoin. Subsequently, intermediate **4** is attacked by β-naphthol to produce complex **6**. Finally, an elimination of water from **6** affords product **3**.



Scheme 2. Proposed mechanism.

The ^{1}H NMR spectrum of **3a** exhibited two sharp singlets readily recognized as arising from a methyl group ($\delta = 2.12$ ppm), a CH group ($\delta = 6.78$ ppm), and a multiplet for the aromatic ($\delta = 7.14$–7.98 ppm) protons. The ^{1}H and ^{13}C NMR spectra of **3b–g** are similar to those of **3a** except for the aryl moieties, which exhibited characteristic signals with appropriate chemical shifts. The structural assignments of compounds **3a–g** made on the basis of their NMR spectra were supported by their IR spectra.

3. Conclusions

The reaction between thiohydantoins, β-naphthol, and aromatic aldehydes provides a simple one-pot synthesis of imidazo[2,1-b]naphtho[1,2-e][1,3]thiazin-10-ones of potential synthetic and pharmaceutical interest. The present procedure has the advantage that the reaction is performed under neutral conditions, and the starting material can be used without any modification. This reaction is simple, gives high yields, is eco-friendly, and does not require chromatographic purification.

4. Experimental

Aldehyde and β-naphthol were obtained from Fluka and were used without further purification. 5,5-Diarylthiohydantoins were prepared by known methods.[14,15] Melting points (uncorrected) were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, N, and S were performed using a Heraeus CHN-S-Rapid analyzer. The experimental data were in good agreement with the calculated values. ^{1}H and ^{13}C NMR spectra (DMSO-d_6) were measured with a Bruker DRX-360 Avance spectrometer. IR spectra were recorded on a Shimadzu IR-460 spectrometer.

4.1. *General procedure for the preparation of 9,9-diphenyl-12-aryl-9H-imidazo[2,1-b] naphtho[1,2-e][1,3]thiazin-10(12H)-one 3*

A mixture of the aldehyde (1 mmol), thiohydantoin (1 mmol), β-naphthol (1 mmol) and catalytic amount of *p*-TSA (0.1 mmol) was stirred at 120°C for 3 h. Completion of the reaction was indicated by TLC. The reaction was cooled to room temperature, then ethylacetate (5 mL) was added and the mixture stirred for 5 min. The solid obtained was removed by filtration and recrystallized from ethanol.

4.1.1. *9,9-diphenyl-12-(p-tolyl)-9H-imidazo[2,1-b]naphtho[1,2-e][1,3]thiazin-10(12H)-one (**3a**)*

Red powder; m.p.: 200–203°C; yield: 3.6 g (72%). IR (KBr) (ν_{max}/cm^{-1}):1702 (C=O), 1671 (C=N). MS (EI) m/z 496.16 (M^+, > 2). Anal. Calcd (%) for $C_{33}H_{24}N_2OS$ (496.62): C, 79.81; H, 4.87; N, 5.64; S, 6.46. Found: C, 79.79; H, 4.86; N, 5.65; S, 6.45. ^{1}H-NMR (360 MHz, DMSO-d_6): $\delta = 2.12$ (3 H, s, Me), 6.78 (1 H, s, CH), 7.14–7.98 (20 H, m, Ar). ^{13}C NMR (90 MHz, DMSO-d_6): $\delta = 21.3(CH_3)$, 35.7 (CH), 73.0 (C), 123.8, 125.0, 125.9, 126.3, 126.6, 127.5, 128.2, 128.5, 128.8, 129.1, 129.4, 129.7, 129.9, 130.1, 130.3, 130.7, 131.9, 132.6, 134.9, 138.2, 142.2, 146.0, 166.2 (C=O), 186.1 [NC(S)N].

4.1.2. *12-(4-chlorophenyl)-9,9-diphenyl-9H-imidazo[2,1-b]naphtho[1,2-e][1,3]thiazin-10(12H)-one (**3b**)*

Yellow powder; m.p.: 208°C; yield: 4.1 g (79%). IR (KBr) (ν_{max}/cm^{-1}):1723 (C=O), 1657 (C=N), 722 (C–Cl). Anal. Calcd (%) for $C_{32}H_{21}ClN_2OS$ (517.04): C, 75.34; H, 4.09; N, 5.42; S, 6.20. Found: C, 75.32; H, 4.08; N, 5.43; S, 6.21. ^{1}H-NMR (360 MHz, DMSO-d_6): $\delta = 6.98$ (1 H, s, CH), 7.14–7.68 (20 H, m, Ar). ^{13}C NMR (90 MHz, DMSO-d_6): $\delta = 37.5$ (CH), 73.2 (C), 124.1, 125.0, 125.9, 126.0, 126.8, 127.0, 128.1, 128.4, 128.7, 128.9, 129.2, 129.3, 129.6, 129.9, 130.2, 130.5, 130.6, 130.9, 131.7, 132.6, 134.9, 142.2, 146.2, 184.2 (C=O), 192.7 [NC(S)N].

4.1.3. *12-(4-nitrophenyl)-9,9-diphenyl-9H-imidazo[2,1-b]naphtho[1,2-e][1,3]thiazin-10(12H)-one (**3c**)*

Yellow powder; m.p.: 328°C; yield: 4.6 g (87%). IR (KBr) (ν_{max}/cm^{-1}): 1743 (C=O), 1660 (C=N), 1495, 1332 (NO_2). MS (EI) m/z 527.13 (M^+, > 2). Anal. Calcd (%) for $C_{32}H_{21}N_3O_3S$ (527.59): C, 72.85; H, 4.01; N, 7.96; S, 6.08. Found: C, 72.87; H, 4.02; N, 7.95; S, 6.10. ^{1}H-NMR (360 MHz, DMSO-d_6): $\delta = 6.96$ (1 H, s, CH), 7.49–8.73 (20 H, m, Ar). ^{13}C NMR (90 MHz, DMSO-d_6): $\delta = 35.7$ (CH), 73.0 (C), 122.6, 124.2, 125.2, 125.6, 126.1, 126.4, 126.9, 127.7, 128.2, 128.5, 128.6, 128.9, 129.2, 129.5, 129.8, 130.1, 131.1, 132.3, 132.6, 134.8, 142.1, 142.4, 146.3, 149.1, 153.1, 173.7 (C=O), 190.9 [NC(S)N].

4.1.4. *12-(4-methoxyphenyl)-9,9-diphenyl-9H-imidazo[2,1-b]naphtho[1,2-e][1,3]thiazin-10(12H)-one (**3d**)*

Red powder; m.p.: 343°C; yield: 3.2 g (63%). IR (KBr) (ν_{max}/cm^{-1}): 1698 (C=O), 1654 (C=N). Anal. Calcd (%) for $C_{33}H_{24}N_2O_2S$ (512.62): C, 77.32; H, 4.72; N, 5.46; S, 6.26. Found: C, 77.30; H, 4.73; N, 5.45; S, 6.26. ^{1}H-NMR (360 MHz, DMSO-d_6): $\delta = 3.33$ (3 H, s, OMe), 6.98 (1 H, s, CH), 7.13–7.52(20 H, m, Ar).

4.1.5. *12-(4-hydroxyphenyl)-9,9-diphenyl-9H-imidazo[2,1-b]naphtho[1,2-e][1,3]thiazin-10(12H)-one (**3e**)*

Red powder; m.p.: 187°C; yield: 4.2 g (84%). IR (KBr) (ν_{max}/cm^{-1}): 3440 (OH), 1712 (C=O), 1649 (C=N). Anal. Calcd (%) for $C_{32}H_{22}N_2O_2S$ (498.59): C, 77.09; H, 4.45; N, 5.62; S, 6.43. Found: C, 77.10; H, 4.45; N, 5.61; S, 6.42. ^{1}H-NMR (360 MHz, DMSO-d_6): $\delta = 6.55$ (1 H, s, CH), 6.97–7.95 (20 H, m, Ar), 8.65 (1 H, br s, OH). ^{13}C NMR (90 MHz, DMSO-d_6): $\delta = 36.2$ (CH), 73.5 (C), 117.1, 123.8, 125.0, 125.9, 126.2, 126.7, 127.5, 128.1, 128.3, 128.6, 128.7, 129.1, 129.5, 129.7, 129.8, 130.6, 130.8, 132.5, 134.9, 138.2, 142.1, 156.0, 159.8, 176.6 (C=O), 193.3 [NC(S)N].

4.1.6. *12-(2,4-dihydroxyphenyl)-9,9-diphenyl-9H-imidazo[2,1-b]naphtho[1,2-e][1,3]thiazin-10(12H)-one (**3f**)*

Red oil; yield: 4.6 g (89%). IR (KBr) (ν_{max}/cm^{-1}): 3427 (OH), 1731 (C=O), 1678 (C=N). Anal. Calcd (%) for $C_{32}H_{22}N_2O_3S$ (514.59): C, 74.69; H, 4.31; N, 5.44; S, 6.23. Found: C, 74.70; H, 4.32; N, 5.45; S, 6.21. ^{1}H-NMR (360 MHz, DMSO-d_6): $\delta = 6.42$ (1 H, br s, OH), 6.80 (1 H, s, CH), 7.14–7.68 (19 H, m, Ar), 7.85 (1 H, br s, OH). ^{13}C NMR (90 MHz, DMSO-d_6): $\delta = 36.0$ (CH), 73.2 (C), 106.0, 110.6, 113.1, 123.8, 125.0, 125.9, 126.4, 126.8, 127.5, 128.2, 128.3, 128.7, 128.9, 129.1, 129.6, 130.0, 130.5, 131.2, 131.8, 132.4, 135.0, 138.2, 142.1, 156.1, 156.9, 170.6 (C=O), 184.8 [NC(S)N].

4.1.7. *12-(4-fluorophenyl)-9,9-diphenyl-9H-imidazo[2,1-b]naphtho[1,2-e][1,3]thiazin-10(12H)-one (**3g**)*

Orange powder; m.p.: 213-215°C; yield: 4.1 g (83%). IR (KBr) (ν_{max}/cm^{-1}): 1709 (C O), 1648 (C N), 1198 (C F). Anal. Calcd (%) for $C_{32}H_{21}FN_2OS$ (500.59): C, 76.78; H, 4.23; N, 5.60; S, 6.41. Found: C, 76.80; H, 4.22; N, 5.59; S, 6.41. ^{1}H-NMR (360 MHz, DMSO-d_6): $\delta = 6.82$ (1 H, s, CH), 7.12–8.04 (20 H, m, Ar).

4.1.8. *12-(5-bromo-2-hydroxyphenyl)-9,9-diphenyl-9H-imidazo[2,1-b]naphtho [1,2-e][1,3]thiazin-10(12H)-one (**3h**)*

Red powder; m.p.: 190–192°C; yield: 3.98 g (69%). IR (KBr) (ν_{max}/cm^{-1}): 1698 (C=O), 1665 (C=N), 652 (C Br). Anal. Calcd (%) for $C_{32}H_{21}BrN_2O_2S$ (577.49): C, 66.55; H, 3.67; N, 4.85; S, 5.55. Found: C, 66.54; H, 3.66; N, 4.87; S, 6.56. ^{1}H-NMR (360 MHz, DMSO-d_6): $\delta = 6.51$ (1 H, s, OH), 6.84 (1 H, s, CH), 7.14–8.23 (19 H, m, Ar).

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