Synthesis of *N*-(3-alkyl-4-phenyl-3*H*-thiazol-2-ylidene)benzamide derivatives by reaction of phenacyl bromide and aroyl isothiocyanates in the presence of primary amines

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A three-component and one-pot reaction between phenacyl bromide and aroyl isothiocyanates in the presence of primary amines gave *N*-(3-alkyl-4-phenyl-3*H*-thiazol-2-ylidene)benzamide derivatives in good yields.

Keywords: phenacyl bromide, aroyl isothiocyanates, *N*-(3-alkyl-4-phenyl-3*H*-thiazol-2-ylidene)benzamides, primary amines

A central objective in synthetic organic chemistry has been to develop efficient syntheses of biologically active compounds with potential application in the pharmaceutical or agrochemical industries. Thiazoles occupy a prominent position among heterocycles. In nature, the thiazolium ring is the chemically active centre in the coenzyme derived from vitamin B_1 (thiamin). A large number of thiazoles obtained from microbial and marine origins exhibit important biological effects such as antitumor, antifungal, antibiotic, and antiviral activities.[1] Synthetic thiazoles have also been shown to exhibit a wide variety of biological activities,[2] while others have found application as liquid crystals[3] and cosmetic sunscreens.[4] The classical method for the synthesis of thiazoles is the Hantzsch process, in which a α-haloketone is condensed with a thioamide.[5] Other methods have been reported for the synthesis of thiazoles.[6–12] As a part of studies on the development of new routes in organic synthesis,[13–19] I now report an efficient one-pot synthesis of *N*-(3-alkyl-4-phenyl-3*H*-thiazol-2-ylidene)benzamide derivatives employing readily available starting materials.

Results and discussion

Reaction between aroyl isothiocyanates **1** and phenacyl bromide **2** in the presence of primary amines **3** gave *N*-(3-alkyl-4-phenyl-3*H*-thiazol-2-ylidene)benzamide derivatives **4** in good yields (Scheme 1).

The structures of compounds **4a–f** were confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The mass spectra of these compounds displayed molecular ion peaks at appropriate *m/z* values. The ^{1}H NMR spectrum of **4a** in $CDCl_3$ showed two singlets for the methylene (δ = 5.43) and methine (δ = 6.47) protons. Aromatic protons resonate between 7.06 and 7.42 ppm as multiplets. The ^{13}C NMR spectrum of **4a** showed 17 signals in agreement with the proposed structure. The IR spectrum of compound **4a** also supported the suggested structure. A tentative mechanism for this transformation is proposed in Scheme 2.

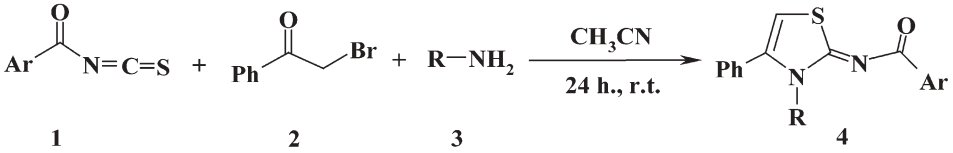
It is reasonable to assume that unsymmetrical thiourea **5** results from the initial addition of the primary amines **3** to aroyl isothiocyanates **1**. Thiourea **5** is alkylated by phenacyl bromide **2** to intermediate **6**, which undergoes cyclisation to generate **7**. Dehydration of intermediate **7** affords product **4**.

Experimental

All melting points are uncorrected. Elemental analyses were performed using a Heraeus CHN–O–rapid analyser. Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C spectra were recorded on Bruker DRX-500 Avance spectrometer in $CDCl_3$ using TMS as the internal standard. Chemicals were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

General procedure

Phenacyl bromide (1 mmol) was added dropwise to a magnetically stirred solution of primary amines (1 mmol) and aroyl isothiocyanates (1 mmol) in 15 mL acetonitrile at room temperature. The reaction



1 2 3 4

4	R	Ar	*Yield%
a	$C_6H_5CH_2$	C_6H_5	82
b	$C_6H_5CH_2$	4-ClC_6H_4	73
c	$C_6H_5CH_2$	4-$NO_2C_6H_4$	71
d	n-Bu	C_6H_5	80
e	n-Bu	4-Cl C_6H_4	75
f	n-Bu	4-$NO_2C_6H_4$	74

* Isolated yields

Scheme 1 Three-component reaction between aroyl isothiocyanates, primary amines and phenacyl bromide.

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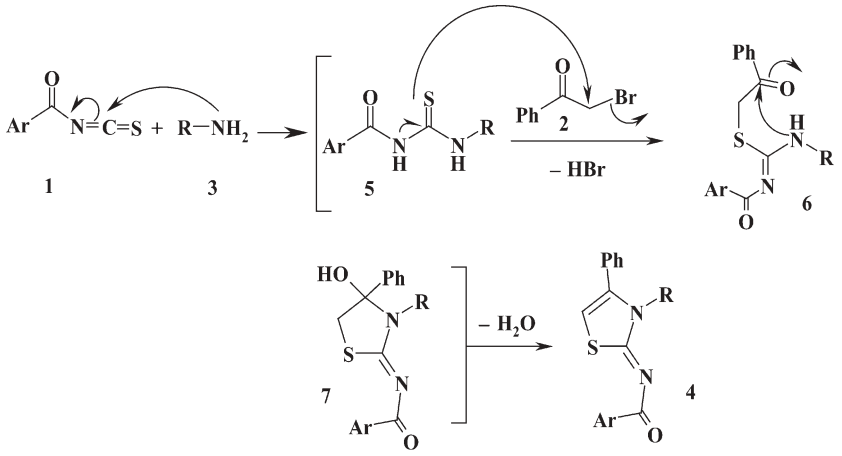

Scheme 2 Suggested mechanism for formation of compound **4**.

mixture was then stirred for 24 h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography using hexane-ethyl acetate as eluent. The solvent was removed under reduced pressure to afford the product.

N-(3-Benzyl-4-phenyl-3H-thiazol-2-ylidene)benzamide (**4a**): Cream powder, m.p. 145–149 °C, IR (KBr) (ν_{max} cm^{-1}): 1595, 1477, 1353. Anal. Calcd for $C_{23}H_{18}N_2OS$: C, 74.57; H, 4.90; N, 7.56. Found: C, 74.65; H, 4.83; N, 7.40%. MS (*m/z*, %): 370 (5). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.43 (2H, s, CH_2), 6.47 (1H, s, CH), 7.06–7.42 (15H, m, 15CH aromatic) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 47.85 (CH_2), 106.71 (CH), 123.83 (C), 127.56, 128.32, 128.45, 129.13, 129.78, 130.15, 131.32, 131.87, 132.46, 133.38, 135.25 and 135.32 (aromatic moiety), 170.28 (C=N), 177.83 (C=O) ppm.

N-(3-Benzyl-4-phenyl-3H-thiazol-2-ylidene)4-chlorobenzamide (**4b**): Cream powder, m.p. 153–156 °C, IR (KBr) (ν_{max} cm^{-1}): 1598, 1472, 1350. Anal. Calcd for $C_{23}H_{17}ClN_2OS$: C, 68.22; H, 4.23; N, 6.92. Found: C, 68.10; H, 4.30; N, 6.74%. MS (*m/z*, %): 404 (3). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.56 (2H, s, CH_2), 6.54 (1H, s, CH), 7.11 (2H, d, $^3J_{HH}$ = 7.8 Hz, 2CH), 7.48 (2H, d, $^3J_{HH}$ = 7.8 Hz, 2CH), 7.05–7.44 (10H, m, 10CH aromatic) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 48.06 (CH_2), 108.55 (CH), 123.94 (C), 127.48, 128.22, 128.57, 129.28, 129.81, 130.09, 131.57, 131.82, 132.35, 133.32, 135.17 and 142.23 (aromatic moiety), 170.06 (C=N), 178.18 (C=O) ppm.

N-(3-Benzyl-4-phenyl-3H-thiazol-2-ylidene)4-nitrobenzamide (**4c**): Cream powder, m.p. 123–126 °C, IR (KBr) (ν_{max} cm^{-1}): 1599, 1483, 1352. Anal. Calcd for $C_{23}H_{17}N_3O_3S$: C, 66.49; H, 4.12; N, 10.11. Found: C, 66.40; H, 4.03; N, 10.23%. MS (*m/z*, %): 415 (9). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.58 (2H, s, CH_2), 6.65 (1H, s, CH), 7.54 (2H, d, $^3J_{HH}$ = 8.5 Hz, 2CH), 8.21 (2H, d, $^3J_{HH}$ = 8.5 Hz, 2CH), 7.07–7.46 (10H, m, 10CH aromatic) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 47.98 (CH_2), 107.81 (CH), 124.07 (C), 127.48, 128.22, 128.57, 129.28, 129.81, 130.09, 131.57, 131.82, 132.35, 133.32, 135.17 and 142.23 (aromatic moiety), 170.25 (C=N), 178.26 (C=O) ppm.

N-(3-Butyl-4-phenyl-3H-thiazol-2-ylidene)benzamide (**4d**): Cream powder, m.p. 132–135 °C, IR (KBr) (ν_{max} cm^{-1}): 1601, 1478, 1351. Anal. Calcd for $C_{20}H_{20}N_2OS$: C, 71.40; H, 5.99; N, 8.33. Found: C, 71.50; H, 5.85; N, 8.40%. MS (*m/z*, %): 336 (7). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.82 (3H, t, $^3J_{HH}$ = 7.4 Hz, CH_3), 1.23–126 (2H, m, CH_2), 1.65–168 (2H, m, CH_2), 4.20 (2H, t, $^3J_{HH}$ = 7.4 Hz, CH_2), 6.52 (1H, s, CH), 7.06–7.45 (10H, m, 10CH aromatic) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.11 (CH_3), 20.16 (CH_2), 30.54 (CH_2), 47.52 (CH_2), 107.28 (CH), 124.32 (C), 128.45, 129.72, 130.17, 131.30, 131.74, 132.42, 135.23 and 135.38 (aromatic moiety), 168.35 (C=N), 174.58 (C=O) ppm.

N-(3-Butyl-4-phenyl-3H-thiazol-2-ylidene)4-chlorobenzamide (**4e**): Cream powder, m.p. 117–120 °C, IR (KBr) (ν_{max} cm^{-1}): 1599, 1480, 1355. Anal. Calcd for $C_{20}H_{19}ClN_2OS$: C, 64.77; H, 5.16; N, 7.55. Found: C, 64.90; H, 5.12; N, 7.60%. MS (*m/z*, %): 370 (5). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90 (3H, t, $^3J_{HH}$ = 7.4 Hz, CH_3), 1.28–131 (2H, m, CH_2), 1.73–175 (2H, m, CH_2), 4.22 (2H, t, $^3J_{HH}$ = 7.4 Hz, CH_2), 6.56 (1H, s, CH), 7.14 (2H, d, $^3J_{HH}$ = 7.8 Hz, 2CH), 7.46 (2H, d, $^3J_{HH}$ = 7.8 Hz, 2CH), 7.06–7.43 (5H, m, 5CH aromatic) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 15.08 (CH_3), 20.28 (CH_2), 30.75 (CH_2), 47.58 (CH_2), 108.50 (CH), 124.45 (C), 128.54, 129.85, 130.14, 131.52, 131.80, 132.37, 135.26 and 142.20 (aromatic moiety), 169.03 (C=N), 174.55 (C=O) ppm.

N-(3-Butyl-4-phenyl-3H-thiazol-2-ylidene)4-nitrobenzamide (**4f**): Cream powder, m.p. 137–140 °C, IR (KBr) (ν_{max} cm^{-1}): 1600, 1484, 1357. Anal. Calcd for $C_{20}H_{19}N_3O_3S$: C, 62.98; H, 5.02; N, 11.02. Found: C, 63.10; H, 5.15; N, 11.14%. MS (*m/z*, %): 381 (11). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (3H, t, $^3J_{HH}$ = 7.4 Hz, CH_3), 1.27–134 (2H, m, CH_2), 1.72–176 (2H, m, CH_2), 4.28 (2H, t, $^3J_{HH}$ = 7.4 Hz, CH_2), 6.67 (1H, s, CH), 7.56 (2H, d, $^3J_{HH}$ = 8.5 Hz, 2CH), 8.25 (2H, d, $^3J_{HH}$ = 8.5 Hz, 2CH), 7.07–7.48 (5H, m, 5CH aromatic) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 15.13 (CH_3), 20.34 (CH_2), 30.85 (CH_2), 47.63 (CH_2), 108.53 (CH), 124.57 (C), 128.56, 129.88, 130.22, 131.58, 131.85, 132.43, 135.28 and 142.36 (aromatic moiety), 170.39 (C=N), 174.63 (C=O) ppm.

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References

1 J.R. Lewis, *Nat. Prod. Rep.*, 1996, **13**, 435.
2 J.V. Metzger, *Thiazole and its derivatives*. John Wiley & Sons, New York, 1979.
3 A.A. Kiryanov, P. Sampson and A. Seed, *J. Org. Chem.*, 2001, **66**, 7925.
4 T. Bach and S. Heuser, *Tetrahedron Lett*., 2000, **41**, 1707.
5 R.H. Wiley, D.C. England and L.C. Behr, *Organic reactions*. John Wiley, New York, 1951; vol. 6, p. 367.
6 J.S. Carter, D.J. Rogier, M.J. Graneto, K. Seibert, C.M. Koboldt, Y. Zhang and J.J. Talley, *Biorg. Med. Chem. Lett.*, 1999, **9**, 1167.
7 R.M. Mohareb, N.I. Abdel-Sayed and S.M. Sherif, *Phosphorus, Sulfur Silicon Relat. Elem*., 1991, **66**, 191.
8 I. Yavari, Z. Hossaini, S. Seyfi and F. Shirgahi-Talari, *Helv. Chim. Acta*, 2008, **91**, 1177.
9 I. Yavari, S.Z. Sayyed-Alangi, R. Hajinasiri and H. Sajjadi-Ghotbabadi, *Monatsch. Chem.*, 2009, **140**, 209.
10 I. Yavari, Z. Hossaini, F. Shirgahi-Talari and S. Seyfi, *Synlett*, 2008, 1631.
11 I. Yavari, S. Ali-Asgari, K. Porshamsian and M. Bagheri, *J. Sulfur Chem.* 2007, **28**, 477.
12 I. Yavari, M. Ghazvini, A.S. Shahvelayati and M.M. Ghanbari, *Phosphorus, Sulfur Silicon Relat. Elem*., 2011, **186**, 134.
13 M.H. Mosslemin, M. Anary-Abbasinejad, A. Hassanabadi and M.A. Bagheri, *J. Sulfur. Chem*., 2010, **31**, 135.
14 A. Hassanabadi, M.H. Mosslemin and S.E. Tadayonfar, *J. Chem. Res*., 2011, **35**, 29.
15 A. Hassanabadi, M.H. Mosslemin, M. Anary-Abbasinejad, M.R. Hosseini-Tabatabaei, H. Mahmoudian and S.E. Tadayonfar, *J. Sulfur. Chem*., 2011, **32**, 355.
16 R. Mohebat, M.H. Mosslemin, A. Dehghan-Darehshiri and A. Hassanabadi, *J. Sulfur. Chem*., 2011, **32**, 557.
17 M. Anary-Abbasinejad, A. Hassanabadi and Z. Khaksari, *Synth. Commun.* 2012, **42**, 204.
18 M. Anary-Abbasinejad, H. Dehghanpour Farashah, A. Hassanabadi, H. Anaraki-Ardakani and N. Shams, *Synth. Commun.*, 2012, **42**, 1877.
19 M. Anary-Abbasinejad, E. Poorhassan and A. Hassanabadi, *Synlett*, 2009, **12**, 1929.