An efficient synthesis of novel dihydrothiazol-2-yl-amides via cyclisation of propargylic carbamothioyl-amides

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An efficient protocol is described for the versatile synthesis of novel dihydrothiazol-2-yl-amide derivatives via the regioselective 5-exo-dig heterocyclisation of *N*-propargyl carbamothioyl-amides in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) in refluxing ethanol. All products were obtained in good yields and short reaction time (10–30 min).

Keywords: DABCO, dihydrothiazol-2-yl-amides, 5-exo-dig, carbamothioyl-amides

The number of publications on the synthesis and application of heterocyclic compounds reveals that they play a crucial role in drug discovery.[1] Thiazole derivatives[2] are found in a large number of synthetic compounds with remarkable biological properties[3] and in naturally occurring products such as aeruginazole A.[4] Thiazoles are attractive pharmacophores for the medicinal chemists to design new compounds with promising biological activities. Consequently, there is a continuing demand for practical routes towards preparing these versatile derivatives.

In this study, we concentrated on dihydrothiazol-2-yl-amides, which have not been widely described in the literature, from both synthetic and biological points of view.[5–7] The dihydrothiazole skeleton is the core element of diverse natural products such as (–)-thiangazole;[8]a naturally-occurring HIV-1 inhibitor, tantazole B,[9] and mirabazole B.[10] Bioactive derivatives have been synthesised. For instance, 2-arylimino-2,3-dihydrothiazole derivatives with significant antimicrobial, antihypertensive, and anticonvulsant activities were prepared by Omar and Eshba.[11] In Chen's work, several 2-substituted 4,5-dihydrothiazole-4-carboxylic acids, MBL inhibitors, were synthesised.[12] A series of 2-(*N*-aryl-*N*-aroyl)amino-4,5-dihydrothiazole derivatives were prepared by Saxena that showed satisfactory antithrombotic activity *in vivo*.[13]

The intramolecular cyclisation of suitably functionalised alkenes has provided practical synthetic procedures leading to the formation of substituted sulfur- and nitrogen-containing heterocycles. Propargylic (thio)amides are one of the suitable precursors tolerating ring closure reaction to give the corresponding five or six membered heterocyclic compounds. A literature survey revealed that the corresponding transformations were catalysed by transition metals and recently various complexes of Ag, Au, Cu, Mo and W have been utilised for the above mentioned reactions.[14–18] In this area, Hashmi and co-workers have investigated multilateral aspects of these cyclisation reactions comprehensively.[19,20]

These reports led us to devise an efficient protocol for the synthesis of dihydrothiazol-2-yl-amide derivatives *via* an intramolecular cyclisation of *N*-propargyl carbamothioyl-amides as part of our research interest in the synthesis of novel heterocycles and bioactive molecules.[21,22] The title compounds **2** were synthesised using *N*-propargyl carbamothioyl-amides **1** in the presence of DABCO in refluxing ethanol (Scheme 1).

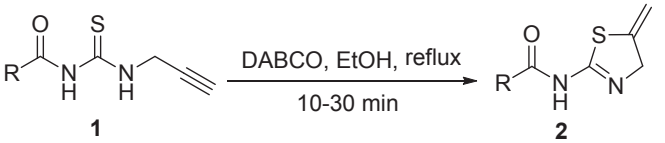
Results and discussion

A series of *N*-propargyl carbamothioyl-amides **1** were conveniently synthesised using different acid chloride derivatives, ammonium thiocyanate, and propargylamine.[23] At first, the cyclisation reaction of 3-nitro-*N*-(prop-2-yn-1-ylcarbamothioyl)benzamide **1d** was selected as a model reaction. It was clear that two ring closure modes were possible in the substrate: (i) 5-exo-dig and (ii) 5-endo-dig. Hashmi examined the cyclisation of propargylic amides and demonstrated that the mode of cyclisation is related to the substituents on triple bond and 5-exo-dig is observed in the case of terminal alkynes.[19]

In our experiments, we found that using base was essential. Depending on the base, solvent, and temperature; the product was obtained in different yields. Interestingly, as we expected, 5-exo-dig mode cyclisation was predominant in all conditions and only the corresponding product, *N*-(5-Methylene-4,5-dihydrothiazol-2-yl)-3-nitrobenzamide **2d** was formed (Table 1, entry 4). Various solvents like EtOH, CH_3CN, and MeOH as well as different bases such as potassium hydroxide (KOH), potassium carbonate (K_2CO_3), 1,4-diazabicyclo[2.2.2]octane (DABCO), and 4-dimethylaminopyridine (DMAP) were examined. Some results are summarised in Table 2. We found that refluxing ethanol and DABCO gave the best conditions to obtain compound **2d** in good yield (77%) and shorter reaction time (20 min).

To confirm the structure, the product was completely characterised by IR spectroscopy, analysis of the mass spectrometric fragmentation pattern and ^1H, and ^{13}C NMR spectra.

The IR spectrum of compound **2d** showed characteristic absorption bands at 3447 and 1614, 1528, 1348 cm^{-1} assigned to (NH), (C=O) and (NO_2), respectively. The MS peak (*m/z* 263) corresponding to the molecular ion, was observed in accordance with calculated mass for $C_{11}H_9N_3O_3S$. ^1H NMR spectrum of



Scheme 1

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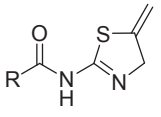
Table 1 Synthesis of dihydrothiazol-2-yl-amide derivatives **2a–j**



2a–j

Entry	R	Product **2**	M.p./°C	Time/min	Yield/%[a]
1	2-Cl-C_6H_4	**2a**	218–220	10	80
2	3-Cl-C_6H_4	**2b**	200–202	15	77
3	4-Cl-C_6H_4	**2c**	216–218	10	75
4	3-NO_2-C_6H_4	**2d**	222–224	20	77
5	4-NO_2-C_6H_4	**2e**	>270	10	80
6	2-Me-C_6H_4	**2f**	145–147	30	70
7	3-Me-C_6H_4	**2g**	126–128	30	70
8	4-MeO-C_6H_4	**2h**	181–183	30	76
9	2-Furyl	**2i**	155–157	20	68
10	2-Thiophene	**2j**	>270	20	65

[a]Isolated yield.

2d consisted of a single signal at 4.46 ppm assigned to the NCH_2 and a multiplet signal around 5.34–5.36 ppm having two protons indicating $=CH_2$ group (in some derivatives, they were observed as two doublet signals with small coupling constants). Four protons associated with the aromatic rings were observed around 7.78–8.86 ppm and the broad singlet signal at 10.21 ppm was assigned to the NH group. As expected, the ^{13}C spectrum exhibited 10 distinct resonances. A signal at 49.5 ppm was related to the aliphatic carbon, NCH_2. Seven aromatic carbons signals were observed around 106.3–141.8 ppm and two signals at 147.8 and 171.8 ppm were related to C=N and C=O groups, respectively.

Satisfied with these results, we explored the limitations of this reaction and investigated the cyclisation reaction of various *N*-propargyl carbamothioyl-amides **1** (Table 1). Note that all precursors containing both electron-donating and electron-withdrawing substituents tolerated 5-exo-dig cyclisation and all expected dihydrothiazol-2-yl-amides **2** were obtained in good yields and short reaction time (10–30 min).

The proposed mechanism is shown in Scheme 2. The acidic N–H proton of *N*-propargyl carbamothioyl-amides **1** is removed by DABCO to allow to the intramolecular nucleophilic attack of sulfur on triple bond (5-exo-dig ring closure, formation of **3**). Then proton transfer and isomerisation gave the title compounds **2**. The probability of isomerisation of **3** to **2** would be greatly enhanced by the appearance of the NH signal at high field in ^1H NMR spectra of products.

Table 2 Investigation of various conditions for the synthesis of **2d**

Entry	Solvent	Base	Time	Yield/%[a]
1	EtOH	DABCO	20 min	77
2	EtOH	KOH	70 min	40
3	EtOH	DMAP	24 h	Trace
4	EtOH	K_2CO_3	24 h	Trace
5	CH_3CN	DABCO	2 h	30
6	MeOH	DABCO	2 h	50

[a]Isolated yield.

Conclusion

In conclusion, we developed an effectual synthesis of dihydrothiazol-2-yl-amide derivatives starting from *N*-propargyl carbamothioyl-amide precursors and involving a regioselective 5-exo-dig cyclisation reaction in the presence of DABCO in ethanol at reflux. All the title compounds were prepared in good yields and short reaction time (10–30 min). Despite the reported cyclisation reaction of *N*-propargyl amides described in the literature, the present reaction did not require catalysis by transition metals.

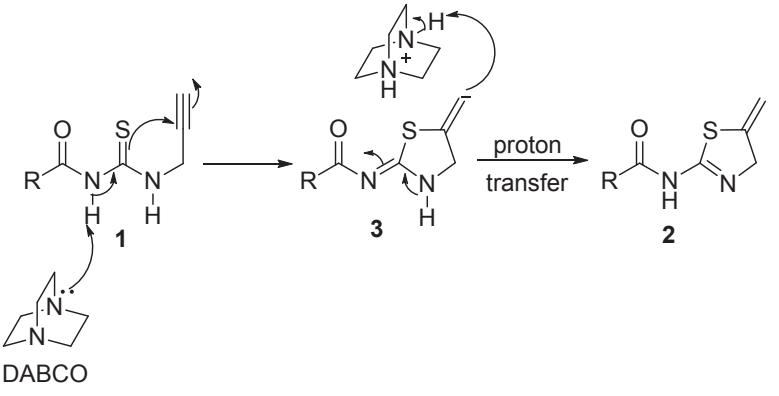
Experimental

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on Bruker FT-500, using TMS as an internal standard. The IR spectra were obtained on a Nicolet Magna FT-IR 550 spectrophotometer (KBr disks). Mass spectra were recorded on an Agilent Technology (HP) mass spectrometer operating at an ionisation potential of 70 eV. Elemental analyses were carried out with a PerkinElmer model 240-C apparatus.

Synthesis of thiazol-2-yl-amide derivatives **2a–j***; general procedure*

A solution of *N*-propargyl carbamothioyl-amide derivative **1** (2 mmol) and DABCO (2 mmol) in ethanol (8 mL) was stirred at reflux for 10–30 min. After completion of the reaction (checked by TLC), the reaction mixture was poured into cold water and the resulting precipitates were filtered off and recrystallised from EtOH to give the pure products.

2-Chloro-N-*(5-methylene-4,5-dihydrothiazol-2-yl)benzamide* **(2a)**: Yield 80%; m.p. 218–220 °C; IR (KBr): 3445, 3144, 1694, 1622, 1584 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): δ_H 11.00 (bs, 1H, NH), 7.64 (dd, J=7.5, 1.5 Hz, 1H, H_6), 7.50 (dd, J=7.5, 1.5 Hz, 1H, H_3), 7.47 (td, J=7.5, 1.5 Hz, 1H, H_4), 7.40 (td, J=7.5, 1.5 Hz, 1H, H_5), 5.31 (d, J=1.2 Hz, 1H, CH), 5.30 (d, J=1.2 Hz, 1H, CH), 4.53 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.4, 156.4, 136.6, 135.3, 131.9, 130.7, 130.4, 130.1, 127.4, 105.5, 55.3; MS *m/z* (%)=254 ([M+2]$^+$, 3), 252 ([M]$^+$, 8), 217 (40), 189 (19), 139 (100), 111 (88), 85 (11), 75 (80), 69 (16), 58 (24), 50 (29). Anal calcd for $C_{11}H_9ClN_2OS$: C, 52.28; H, 3.59; N, 11.09; found: C, 52.07; H, 3.34; N, 10.89%.



Scheme 2

3-Chloro-N-*(5-methylene-4,5-dihydrothiazol-2-yl)benzamide* **(2b)**: Yield 77%; m.p. 200–202 °C; IR (KBr): 3461, 1616, 1538, 1406 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): δ_H 9.90 (bs, 1H, NH), 8.08–8.07 (m, 1H, H_2), 8.01 (d, J=7.8 Hz, 1H, H_6), 7.63 (td, J=7.8, 1.0 Hz, 1H, H_4), 7.52 (t, J=7.8 Hz, 1H, H_5), 5.35 (s, 1H, CH), 5.32 (s, 1H, CH), 4.44 (s, 2H, CH_2); MS *m/z* (%)=254 ($[M+2]^+$, 1), 252 ($[M]^+$, 3), 139 (100), 111 (86), 75 (70), 69 (23), 50 (30). Anal calcd for $C_{11}H_9ClN_2OS$: C, 52.28; H, 3.59; N, 11.09; found: C, 51.96; H, 3.38; N, 11.28%.

4-Chloro-N-*(5-methylene-4,5-dihydrothiazol-2-yl)benzamide* **(2c)**: Yield 75%; m.p. 216–218 °C; IR (KBr): 3207, 1616, 1574, 1538 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): δ_H 9.80 (bs, 1H, NH), 8.07 (d, J=8.5 Hz, 2H, H_2, H_6), 7.54 (d, J=8.5 Hz, 2H, H_3, H_5), 5.34 (s, 1H, CH), 5.31 (s, 1H CH), 4.44 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.6, 142.5, 137.3, 135.1, 131.1, 130.5, 128.8, 106.6, 57.3; MS *m/z* (%)=254 ($[M+2]^+$, 1), 252 ($[M]^+$, 3), 139 (100), 111 (87), 75 (68), 69 (31), 55 (34), 50 (26). Anal calcd for $C_{11}H_9ClN_2OS$: C, 52.28; H, 3.59; N, 11.09; found: C, 52.50; H, 3.73; N, 11.25%.

N-*(5-Methylene-4,5-dihydrothiazol-2-yl)-3-nitrobenzamide* **(2d)**: Yield 77%; m.p. 222–224 °C. IR (KBr): 3447, 1614, 1577, 1528, 1474, 1406, 1348 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 10.21 (bs, 1H, NH), 8.86 (s, 1H, H_2), 8.45 (d, J=8.0 Hz, 1H, H_4), 8.39 (dd, J=8.0, 1.7 Hz, 1H, H_6), 7.78 (t, J=8.0 Hz, 1H, H_5), 5.36–5.34 (m, 2H, =CH_2), 4.46 (s, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 171.8, 147.8, 141.8, 137.9, 134.9, 130.1, 126.3, 123.3, 106.3, 49.5; MS: *m/z* (%)=263 ($[M]^+$, 4), 150 (89), 141 (13), 104 (75), 92 (12), 76 (100), 71 (35), 55 (22), 50 (37). Anal calcd for $C_{11}H_9N_3O_3S$: C, 50.18; H, 3.45; N, 15.96; found: C, 49.95; H, 3.32; N, 16.15%.

N-*(5-Methylene-4,5-dihydrothiazol-2-yl)-4-nitrobenzamide* **(2e)**: Yield 80%; m.p.>270 °C IR (KBr): 3424, 3195, 1616, 1543, 1411, 1351 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 10.10 (bs, 1H, NH), 8.33 (d, J=9.0 Hz, 2H, H_3, H_5), 8.28 (d, J=9.0 Hz, 2H, H_2, H_6), 5.37 (d, J=1.3 Hz, 1H, CH), 5.34 (d, J=1.3 Hz, 1H, CH), 4.46 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.6, 149.9, 141.7, 141.6, 134.6, 130.5, 124.0, 107.2, 49.2. Anal calcd for $C_{11}H_9N_3O_3S$: C, 50.18; H, 3.45; N, 15.96; found: C, 50.36; H, 3.15; N, 16.30%.

2-Methyl-N-*(5-methylene-4,5-dihydrothiazol-2-yl)benzamide* **(2f)**: Yield 70%; m.p. 145–147 °C. IR (KBr): 3435, 3136, 2866, 2795, 1692, 1627, 1514 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, J=7.0 Hz, 1H, H_6), 7.42 (td, J=7.5, 1.3 Hz, 1H, H_4), 7.31–7.28 (m, 2H, H_3, H_5), 5.21 (s, 1H, CH), 5.13 (s, 1H, CH), 4.00 (s, 2H, CH_2), 2.49 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.4, 167.5, 145.4, 137.5, 135.7, 131.4, 131.0, 129.3, 125.9, 105.0, 55.7, 20.8; MS: *m/z* (%)=232 ($[M]^+$, 10), 217 (32), 119 (100), 91 (90), 65 (45). Anal calcd for $C_{12}H_{12}N_2OS$: C, 62.05; H, 5.21; N, 12.06; found: C, 61.88; H, 5.46; N, 11.82%.

3-Methyl-N-*(5-methylene-4,5-dihydrothiazol-2-yl)benzamide* **(2g)**: Yield 70%; m.p. 126–128 °C. IR (KBr): 3430, 3132, 2863, 2795, 1690, 1630, 1520 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.93–7.91 (m, 2H, H_2, H_6), 7.39–7.36 (m, 2H, H_4, H_5), 5.37–5.36 (m, 2H, =CH_2), 4.58 (s, 2H, CH_2), 2.43 (s, 3H, CH_3). Anal calcd for $C_{12}H_{12}N_2OS$: C, 62.05; H, 5.21; N, 12.06; found: C, 62.28; H, 4.92; N, 12.27%.

4-*Methoxy*-N-*(5-methylene-4,5-dihydrothiazol-2-yl)benzamide* **(2h)**: Yield 76%; m.p. 181–183 °C. IR (KBr): 3403, 1601, 1570, 1538 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 9.95 (bs, 1H, NH), 8.04 (d, J=8.9 Hz, 2H, H_2, H_6), 7.00 (d, J=8.9 Hz, 2H, H_3, H_5), 5.30 (d, J=1.1 Hz, 1H, CH), 5.27 (d, J=1.1 Hz, 1H, CH), 4.43 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3). Anal calcd for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87; N, 11.28; found: C, 58.24; H, 4.66; N, 11.05%.

N-*(5-Methylene-4,5-dihydrothiazol-2-yl)furan-2-carboxamide* **(2i)**: Yield 68%; m.p. 155–157 °C. IR (KBr): 3173, 3111, 1615, 1560, 1479 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.58–7.57 (m, 1H, furan), 7.34–7.33 (m, 1H, furan), 6.58–6.55 (m, 1H, furan), 5.33–5.31 (m, 2H, =CH_2), 4.58 (s, 2H, CH_2). Anal calcd for $C_9H_8N_2O_2S$: C, 51.91; H, 3.87; N, 13.45; found: C, 51.73; H, 3.62; N, 13.66%.

N-*(5-Methylene-4,5-dihydrothiazol-2-yl)thiophene-2-carboxamide* **(2j)**: Yield 65%; m.p.>270 °C. IR (KBr): 3429, 3136, 2880, 1609, 1541, 1509 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 9.80 (bs, 1H, NH), 7.80–7.75 (m, 2H, thiophene), 7.17–7.15 (m, 1H, thiophene), 5.33–5.30 (m, 2H, =CH_2), 4.40 (s, 2H, CH_2). Anal calcd for $C_9H_8N_2OS_2$: C, 48.19; H, 3.60; N, 12.49; found: C, 48.31; H, 3.42; N, 12.63%.

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