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GREEN SYNTHESIS OF THIAZOLO [2, 3-a] ISOQUINOLINES USING SILICA SULPHURIC ACID UNDER MICROWAVE IRRADIATION

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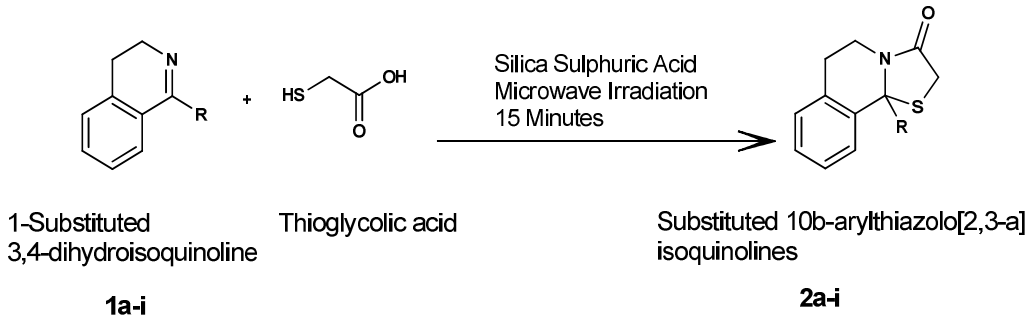
ABSTRACT
The thiazolo [2, 3-a] isoquinoline derivatives were synthesised by condensation reaction between various 3, 4-dihydroisoquinolines with thioglycolic acid using silica sulphuric acid under microwave irradiation. The synthesised compounds were characterised by FT-IR, ^{1}H NMR, ^{13}C NMR, elemental analysis and GC-MS spectroscopy.

KEYWORDS
Microwave irradiation; Silica sulphuric acid; Thiazolo[2,3-a] isoquinolines;Thioglycolic acid.

INTRODUCTION
Heterocyclic compounds are important intermediates in the synthesis of several biologically active compounds[i].The synthesis of structurally diverse and fused heterocycle is the milestone in the field of organic chemistry, pharmaceutical and agrochemical industries [ii.]
Thiazolidinones show anti-HIV,[iii] antimalarial,[iv]anticancer, [v]antibacterial[vi] activities. Currently synthesis of structurally diverse molecules is focused as a part of developing the new drug candidates. The combination of 3,4-dihydroisoquinoline with thiazolidinone ring gives structurally diverse thiazolo [2, 3-a] isoquinolines, a sulphur containing tricyclic alkaloid derivative.
The synthesis of thiazolo[2,3-a] isoquinolines is reported in the literature[vii, viii].The reported methods for synthesis have limitations such as longer reaction time, use of expensive catalysts, solvents and poor yields etc. Therefore there is need to develop simple and rapid method for synthesis of thiazolo[2,3-a] isoquinolines. Thus we report the condensation reaction between various 1-substituted 3,4-dihydroisoquinolines and thioglycolic acid under microwave irradiation using silica sulphuric acid as catalyst.

RESULTS AND DISCUSSION:
The Fischer esterification [ix],synthesis of 1,4-dihydropyridines [x] is reported by using silica sulphuric acid. The condensation reaction between various 1-substituted 3,4-dihydroisoquinolines and thioglycolic acid by using silica sulphuric acid under microwave irradiation gives thiazolo[2,3 -a] isoquinolines in 15 minutes. The method is efficient as reaction completes in short time giving product in good yields.



Scheme 1: Synthesis of Thiazolo [2, 3-a] isoquinolines.

EXPERIMENTAL SECTION:

All the reagents and chemicals were purchased from SD Fine Chemicals, India and used without further purification. Silica gel of commercial source (60–120 mesh) was used for preparation of catalyst. The melting points are uncorrected. The reactions were performed using a Startsynth Microwave Synthesis Labstation model microwave reactor.IR spectra were recorded on Frontier Perkin Elmer IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker AVANCE 300 MHz instrument in $CDCl_3$ using TMS as internal standard. Chemical shifts (δ) are expressed in ppm and coupling constants *J* are given in Hz. The spectral characterization data of synthesized compounds, elemental analysis and spectra are presented in supporting Information file1.

General procedure for preparation of Silica Sulphuric Acid.

Silica gel (60-120mesh) (30.0 g) was taken in two necked round bottom flask. Chlorosulfonic acid (6.0 ml) is added drop wise in 30 minutes time interval. Rapidly generated HCl gas was neutralized by NaOH solution. Once the addition is over, the reaction mixture is shaken for another 30 minutes and kept in desiccator.

General procedure for the synthesis of 1-substituted 3,4-dihydroisoquinolines.

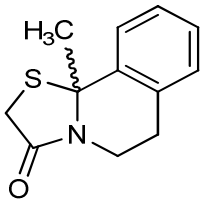
The 1-Substituted 3, 4-dihydroisoquinolines were prepared as reported in the literature.[xi,xii]

General procedure for the synthesis of thiazolo[2,3-a] isoquinolines.(2a-i)

1-Substituted 3, 4-dihydroisoquinoline (0.01mol) **(1a-1i)**, thioglycolic acid (0.02mol) were mixed with silica sulphuric acid (2gm). The reaction mixture was irradiated in microwave for 15 minutes. The completion of reaction was monitored by TLC. After the completion of reaction, 15ml of ethyl acetate was added to reaction mixture and filtered the mixture to remove silica sulphuric acid. Ethyl acetate was recovered under reduced pressure. The crude product obtained was then purified by column chromatography over silica gel (Petroleum ether: Chloroform 70:30) to afford colourless solid of thiazolo[2, 3-a] isoquinolines.(2a-i).

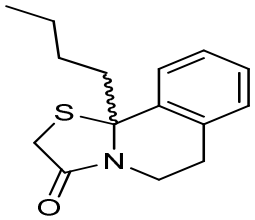
Structure, spectral characterization and elemental analysis of new compounds (2a-i)

Structure :2a



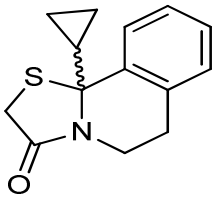
10b-methyl-5, 6-dihydro-2H-thiazolo [2, 3-a] isoquinolin-3(10bH)-one (2a).
White solid, Yield: 72%., M.P:102 ^{0}C.
IR (cm^{-1}): 2978.71, 1666.39, 1405.01, 1298.12, 753.77.
^{1}H NMR ($CDCl_3$): 7.09-7.26 (m, 4H, aromatic), 1.95 (s, 3H, aliphatic), 2.74-2.81 (ddd, 1H, aliphatic *J*=21Hz), 2.95-3.06 (d, 1H, aliphatic *J*=33Hz), 3.13-3.23 (d, 1H, aliphatic *J*=30Hz), 3.59-3.64 (dd, 1H, aliphatic *J*=15Hz), 3.82-3.88 (dd, 1H, aliphatic *J*=18Hz), 4.40-4.47 (ddd, 1H, aliphatic *J*=21Hz).
^{13}C NMR ($CDCl_3$):28.36, 32.63, 34.08, 36.74, 88.70, 125.41, 127.11, 127.60, 129.27, 131.52, 140.49, 169.22.
MS: M^+ at m/z: 219.05.
Elemental Analysis:$C_{12}H_{13}NOS$, Calculated :C (65.72%), H(5.97%), N(6.39%), S(14.62%) Observed :C (65.68%), H(5.93%), N(6.28%), S(14.54%)

Structure: 2b



10b-butyl-5, 6-dihydro-2H-thiazolo [2, 3-a] isoquinolin-3(10bH)-one (2b)
White solid, Yield: 69%. M.P:109 ^{0}C
IR (cm^{-1}):2949.52, 1666.17, 1409.95, 1378.10, 1256.09, 774.21, 634.27.
^{1}H NMR ($CDCl_3$):7.08-7.26 (m, 4H, aromatic), 0.88-0.93 (t, 3H methyl *J*=15Hz), 1.25-1.36 (m, 4H, aliphatic), 2.01-2.07 (ddd, 1H, aliphatic *J*=18Hz), 2.12-2.17 (ddd, 1H, aliphatic *J*=15Hz), 2.79-2.81 (d, 1H, aliphatic *J*=6Hz), 3.02-3.15 (ddd, 1H, aliphatic *J*=39Hz), 3.58-3.63 (dd, 1H aliphatic *J*=15Hz), 3.78-3.84 (dd, 1H aliphatic *J*=18Hz), 4.40-4.47 (ddd, 1H, aliphatic *J*=21Hz).
^{13}C NMR ($CDCl_3$): 14.04, 22.34, 26.04, 27.95, 34.73, 36.86, 44.47, 71.75, 125.55, 126.88, 127.48, 129.18, 131.25, 141.36, 169.57.
MS: M^+ at m/z: 262.10
Elemental Analysis: $C_{15}H_{19}NOS$, Calculated :C (68.93%), H(7.33%), N(5.36%), S(12.27%) Observed: C(68.89%), H(7.26%), N(5.28%), S(12.19%)

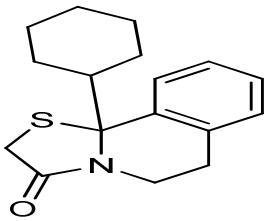
Structure: 2c



10b-cyclopropyl-5, 6-dihydro-2H-thiazolo [2, 3-a] isoquinolin-3(10bH)-one (2c)
White solid, Yield: 72%; M.P: 95^{0}C
IR (cm^{-1}):2921.44, 1657.65, 1451.21, 1409.22, 1028.38, 750.66.
^{1} H NMR ($CDCl_3$): 7.09-7.26 (m, 4H aromatic), 0.48-0.52 (m, 1H aliphatic), 0.53-0.56 (m, 1H aliphatic), 0.65-0.73 (m, 1H aliphatic), 1.25-1.28 (m, 1H, aliphatic), 1.51-1.55 (m, 1H, aliphatic), 2.78-2.85 (m, 1H, aliphatic), 2.99-3.05 (d, 1H, aliphatic *J*=18Hz), 3.46-3.47 (d,

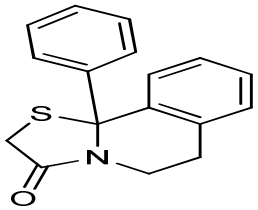
1H, aliphatic *J*=3Hz), 3.50-3.57 (m, 1H, aliphatic), 3.70-3.75 (dd, 1H aliphatic *J*=15Hz), 4.43-4.50 (m, 1H aliphatic).
^{13}C NMR ($CDCl_3$): 1.37, 4.77, 23.08, 28.00, 34.29, 37.30, 72.99, 126.24, 126.54, 127.67, 129.08, 132.01, 139.71, 168.87.
MS: M^+ at m/z: 245.00
Elemental Analysis: $C_{14}H_{15}NOS$, Calculated :C (68.54%), H(6.16%), N(5.71%), S(13.07%) Observed: C(68.42%), H(6.04%), N(5.63%), S(12.98%)

Structure: 2d



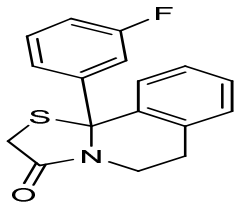
10b-cyclohexyl-5, 6-dihydro-2H-thiazolo[2,3-a]isoquinolin-3(10bH)-one (2d)
White solid, Yield: 76%. M.P: 112^{0}C
IR (cm^{-1}):2926.23, 2021.17, 1666.81, 1452.64, 1410.17, 1226.31, 756.58
^{1}H NMR ($CDCl_3$): 7.10-7.26 (m, 4H, aromatic), 1.54-1.96 (m, 11H, aliphatic), 2.88-2.93 (ddd, 1H, aliphatic *J*=15Hz), 3.02-3.04 (d, 1H, aliphatic *J*=6Hz), 3.30-3.35 (ddd, 1H, aliphatic *J*=15Hz), 3.53-3.58 (dd, 1H, aliphatic *J*=15Hz), 3.69-3.74 (dd, 1H aliphatic *J*=15Hz), 4.35-4.42 (m, 1H, aliphatic).
^{13}C NMR ($CDCl_3$):26.00, 26.29, 27.15, 27.83, 34.41, 37.84, 49.40, 75.92, 125.84, 127.24, 127.55, 129.02, 132.12, 139.81, 170.02.
MS: M^+ at m/z: 287
Elemental Analysis: $C_{17}H_{21}NOS$, Calculated :C (71.04%), H(7.36%), N(4.87%), S(11.76%) Observed: C(70.97%), H(7.29%), N(4.79%), S(11.69%)

Structure: 2e



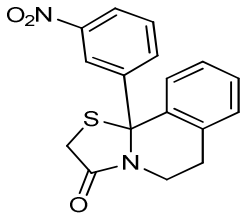
10b-phenyl-5, 6-dihydro-2H-thiazolo [2, 3-a] isoquinolin-3(10bH)-one(2e)
White solid, Yield: 78%. M.P:160 ^{0}C.
IR (cm^{-1}): 2949.18, 1665.15, 1390.02, 1288.30, 761.58, 697.66.
^{1}H NMR ($CDCl_3$): 7.47-7.50 (m, 1H aromatic), 7.15-7.33 (m, 8H aromatic), 2.61-2.67 (ddd, 1H, *J*=18 Hz), 2.99-3.02 (d, 1H, *J*= 9Hz), 3.70-3.76 (dd, 1H, *J*=18Hz), 3.95-4.00 (dd, 1H, *J*= 15Hz), 4.09-4.11 (ddd, 1H, *J*= 6Hz), 4.13-4.15 (ddd, 1H, aliphatic, *J*=6Hz)
^{13}C NMR ($CDCl_3$):27.15, 34.34, 38.14, 73.45, 126.39, 126.87, 127.65, 128.12, 128.25, 128.44, 128.85, 133.44, 138.84, 144.03, 169.79.
MS: M^+ at m/z: 281.05
Elemental Analysis: $C_{17}H_{15}NOS$, Calculated :C (72.57%), H(5.37%), N(4.98%), S(11.40%) Observed: C(72.49%), H(5.26%), N(4.85%), S(11.34%)

Structure : 2f



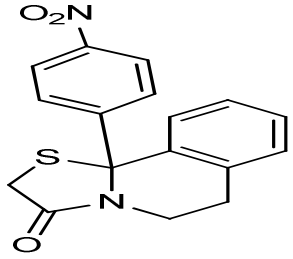
10b-(3-fluorophenyl)-5, 6-dihydro-2H-thiazolo [2, 3-a] isoquinolin-3 (10bH)-one (2f)
White solid, Yield: 74%, M.P:122 ^{0}C
IR (cm^{-1}):2948.19, 1666.03, 1390.18, 1236.61, 755.46
^{1}H NMR ($CDCl_3$):7.46-7.49 (m, 1H aromatic), 6.90-7.02 (m, 1H aromatic),7.15-7.34 (m, 6H aromatic), 2.62-2.68 (ddd, 1H, *J*=18Hz), 3.00-3.02 (d, 1H aliphatic *J*=6Hz), 3.18-3.24 (ddd, 1H, aliphatic *J*=18Hz), 3.70-3.75 (dd, 1H, aliphatic *J*=15Hz), 3.94-3.99 (dd, 1H, aliphatic *J*=15Hz), 4.10-4.18 (ddd, 1H, aliphatic *J*=24Hz)
^{13}C NMR ($CDCl_3$):27.09, 34.19, 38.24, 72.85, 114.08, 114.39, 114.99, 115.27, 122.44, 122.48, 126.57, 127.54, 128.52, 128.96, 129.94, 130.05, 133.40, 138.30, 146.86, 146.95, 161.06, 164.33, 169.76.
MS: M^+ at m/z: 298.97
Elemental Analysis: $C_{17}H_{14}NFOS$, Calculated :C (68.21%), H(4.71%), N(4.68%), S(10.71%)
Observed: C(68.18%), H(4.64%), N(4.57%), S(10.69%)

Structure: 2g



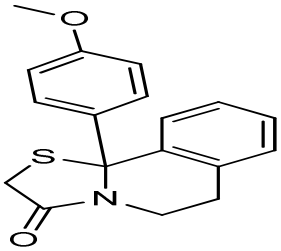
Synthesis of 10b-(3-nitrophenyl)-5, 6-dihydro-2H-thiazolo [2, 3-a] isoquinolin-3 (10bH)-one (2g)
White solid, Yield: 72%, M.P: 153^{0}C
IR (cm^{-1}):2921.20, 1671.04, 1519.49, 1338.97, 1283.30, 770.77, 670.72.
^{1} H NMR ($CDCl_3$): 8.10-8.14(m, 1H, aromatic), 7.19-7.60(m, 7H, aromatic), 2.61-2.68 (ddd, 1H, aliphatic *J*= 24Hz), 3.04-3.06 (d, 1H, aliphatic *J*=6Hz), 3.10-3.14(ddd, 1H, aliphatic *J*=12Hz), 3.74-3.79 (dd, 1H, aliphatic *J*=15), 3.98-4.03 (dd, 1H, aliphatic *J*= 15Hz), 4.17-4.23 (ddd, 1H, aliphatic *J*=18Hz).
^{13}C NMR ($CDCl_3$):27.08, 34.18, 38.28, 72.66, 122.13, 123.21, 126.93, 127.60, 128.92, 129.26, 129.51, 132.80, 133.42, 137.55, 146.77, 148.40, 169.78.
MS: M^+ at m/z: 326.27
Elemental Analysis: $C_{17}H_{14}N_2O_3S$, Calculated :C (62.56%), H(4.32%), N(8.58%), S(9.82%)
Observed: C(62.49%), H(4.28%), N(8.46%), S(9.74%)

Structure: 2h



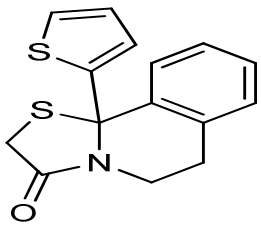
10b-(4-nitrophenyl)-5, 6-dihydro-2H-thiazolo [2, 3-a] isoquinolin-3(10bH)-one (2h)
White solid, Yield: 71%, M.P: 161^{0}C
IR (cm^{-1}):2981.00, 1654.17, 1397.37, 1344.34, 1256.84, 751.06, 632.02.
^{1}H NMR ($CDCl_3$):8.11-8.15 (m, 1H, aromatic), 7.18-7.52 (m, 7H, aromatic), 2.60-2.65 (ddd, 1H, aliphatic *J*=15Hz), 3.02-3.04(d, 1H, aliphatic *J*= 6Hz), 3.14-3.20 (ddd, 1H, aliphatic *J*=18Hz), 3.74-3.79 (dd, 1H, aliphatic *J*=15Hz), 3.95-4.00 (dd,1H, aliphatic, *J*=15Hz), 4.10-4.19 (ddd, 1H, aliphatic *J*= 27Hz)
^{13}C NMR ($CDCl_3$):27.00, 34.07, 38.55, 72.54, 123.74, 126.85, 127.45, 127.75, 128.92, 129.13, 133.47, 137.64, 147.41, 151.20, 169.86.
MS: M^+ at m/z: 325.9
Elemental Analysis: $C_{17}H_{14}N_2O_3S$, Calculated :C (62.56%), H(4.32%), N(8.58%), S(9.82%)
Observed: C(62.48%), H(4.26%), N(8.52%), S(9.76%)

Structure: 2i



10b-(4-methoxyphenyl)-5, 6-dihydro-2H-thiazolo [2, 3-a] isoquinolin-3(10bH)-one (2i)
White solid, Yield: 76%, M.P: 123^{0}C
IR (cm^{-1}):2959.57, 2928.81, 1665.24, 1392.55, 1249.10, 755.71, 604.04.
^{1}H NMR ($CDCl_3$):7.45-7.48 (m, 1H, aromatic), 6.77-7.33 (m, 7H, aromatic), 2.62-2.69 (ddd, 1H, aliphatic, *J*=21Hz), 2.99-3.00 (d, 1H, aliphatic *J*=3Hz), 3.03-3.14 (ddd, 1H, aliphatic *J*=33Hz),3.75-3.77 (dd, 1H, aliphatic *J*=6Hz), 3.94-3.99(dd, 1H, aliphatic *J*=15Hz), 4.11-4.18 (ddd, 1H, 21Hz).
^{13}C NMR ($CDCl_3$):27.19, 34.36, 37.86, 55.32, 73.40, 113.64, 126.32, 127.73, 128.17, 128.57, 128.90, 133.41, 136.05, 139.12, 159.35, 169.62
MS: M^+ at m/z: 311.14.
Elemental Analysis: $C_{18}H_{17}NO_2S$, Calculated :C (69.43%), H(5.50%), N(4.50%), S(10.30%)
Observed: C(69.38%), H(5.42%), N(4.47%), S(10.24%)

Structure: 2j



10b-(thiophen-2-yl)-5,6-dihydro-2H-thiazolo[2,3-a]isoquinolin-3(10bH)-one (2j)
White solid, Yield: 80%, M.P: 117^0C
IR (cm^{-1}):2945.29, 1665.76, 1389.80, 1289.55, 753.82, 650.19.
^{1}H NMR ($CDCl_3$):7.40-7.43 (m, 1H, aromatic),7.13-7.29 (m, 3H,aromatic), 6.60-6.83 (m, 3H, aromatic), 2.75-2.81 (ddd, 1H, aliphatic *J*=18Hz), 3.05-3.07 (d, 1H, aliphatic *J*=6Hz), 3.13-3.21(ddd, 1H, aliphatic, *J*=24Hz), 3.72-3.77 (dd, 1H, aliphatic, *J*=15Hz), 4.01-4.07 (dd, 1H, aliphatic *J*=18Hz), 4.27-4.34 (dd, 1H, aliphatic *J*= 21Hz)
^{13}C NMR ($CDCl_3$):27.57, 34.51, 37.35, 70.14, 126.44, 126.66, 126.98, 127.32, 127.52, 128.38, 129.06, 132.63, 138.65, 150.91, 168.88.
MS: M^+ at m/z: 287.05.
Elemental Analysis: $C_{15}H_{13}NOS_2$, Calculated :C (62.69%), H(4.56%), N(4.87%), S(22.31%)
Observed: C(62.60%), H(4.48%), N(4.79%), S(22.28%)

CONCLUSION

In the current investigation, we have developed a new green and efficient method for the synthesis of Thiazolo[2, 3-a] isoquinolines using silica sulphuric acid under microwave irradiation.

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REFERENCES

(i) John, A. J.; Keith, M.*Heterocyclic Chemistry*, 5th Edition Wiley-Blackwell, (2010)
(ii) Edon, V.; David, T. S.;Jon, T. N.J. Med. Chem., 57, 10257,(2014).
(iii) Jan, B.; Barbara, O-K.; Jan,K. M.;Andrzej,O.Eur.J. Med.Chem.44,303,(2009).
(iv) Fernando, A. R.R.;Rory, N. G-S.; Santiago,V.E.;Alicia,G-B.;Diego, F. T.;Antonio,R. M-F.; Vladimir V. K.Bioorg.& Med. Chem.19, 4562,(2011).
(v) Patel, A. B.;Chikhalia,K.H.;Kumari, P. J. Saudi Chem.Soc.18, 646,(2014).
(vi) Patel, R.N.; Patel, P.V.; Desai, K.R .;Purohit, P.Y.; Nimavat, K.S.;Vyas, K.B. Het. Lett. 2,99(2012).
(vii) Rozwadwoska, M.D.;Agnieszka S.Tetrrahedron 57, 3499(2001).
(viii) William, P.; Unsworth, G. C.; Christiana K.; Richard J. K. T. J. Org. Chem. 79,1368 (2014).
(ix) Rajendran,A.;Karthikeyan, C. Am.Chem.Sci.J.1, 28(2011).
(x) Eskandar,K.;Mohammad, A. Z.;Nadiya, K.;Behzad, S-S.ChemPapers 65, 898 (2011).
(xi) Sreeramulu, N.; Fodor, G . J. Het. Chem.17, 1457 (1980).
(xii) Margarita, A. E.;Alexander, S. K.;Marina, I. S.;Nikolai V. I.;Michael, S.; Nina, N. M.Mendeleev Commun.22, 267 (2012).

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