One-pot synthesis of thiazolo[3,4-*a*]quinoxalines from 1,2-diamines, aryl isothiocyanates and ethyl bromopyruvate

Mohammad Piltan*

Department of Chemistry, Faculty of Science, Sanandaj Branch, Islamic Azad University, Sanandaj, Iran

Some hitherto unreported thiazolo[3,4-*a*]quinoxaline derivatives have been synthesised in excellent yields *via* a one-pot, three-component reaction of benzene-1,2-diamines, ethyl bromopyruvate and aryl isothiocyanates in MeCN, for the first time. The protocol avoids the use of any catalysts or chromatographic separations and provides a wide range of novel thiazolo[3,4-*a*]quinoxalines.

Keywords: thiazolo[3,4-*a*]quinoxalines, ethyl bromopyruvate, 1,2-diaminobenzenes, aryl isothiocyanates

The azolo[*a*]quinoxaline framework has been found to be an integral part of several bioactive compounds.[1,2] For example, compound LU-73068, an anticonvulsant, and the antiallergic drug Dazoquinast are imidazo[1,2-*a*]quinoxaline derivatives, and drugs U-97775 and U-80447, which have a sedative effect, are imidazo[1,5-*a*]-quinoxaline derivatives.[3] However, compared with the well-studied synthesis and properties of the azolo[*a*]quinoxaline system, such as imidazo[1,2-*a*]quinoxaline and imidazo[1,5-*a*]-quinoxaline derivatives, methods for the synthesis of thiazolo[3,4-*a*]quinoxalines remain poorly investigated. Adegoke and Alo reported the first thiazolo[3,4-*a*]quinoxaline system from thiazole derivatives as starting materials, involving intramolecular reductive cyclisation of 4-carboxy- or 4-methoxycarbonyl-3-(2-nitrophenyl)thiazolines, in 1983.[4] Another approach to the design of thiazolo[3,4-*a*]quinoxalines involves the intramolecular acid-catalysed cyclisation of (α-isothioureido-thiocyanato- and xanthahenato).[5–7] Jinbo and co-workers have described cyclisation of 4-chloromethyl-3-(2,3,4-trifluorophenyl) thiazolidine-2-thione with aqueous ammonia in acetonitrile to give the thiazolo[3,4-*a*]quinoxaline system.[2] Recently, Mamedov *et al.* reported the synthesis of thiazolo[3,4-*a*]quinoxalines from 4-hydroxythiazolidines with 1,2-diaminobenzenes in a poor yield of only 15%.[8] These methods are not widely used because these strategies have limitations, such as required additional additives, narrow substrate scopes and low reaction yield. Moreover, these quinoxaline and thiazolidine derivatives are difficult to synthesise. Therefore, the development of more efficient methods for the preparation of thiazolo[3,4-*a*]quinoxalines needs to be investigated. In continuation of my work on the development of efficient protocols for the synthesis of heterocyclic compounds from simple starting materials, such as 1,2-diaminobenzenes,[9–13] Unlike the approaches mentioned above, here I present, a novel approach to the synthesis of thiazolo[3,4-*a*]quinoxaline derivatives *via* a one-pot, three-component reaction of benzene-1,2-diamines, aryl isothiocyanates and ethyl bromopyruvate in excellent yields (Scheme 1).

Results and discussion

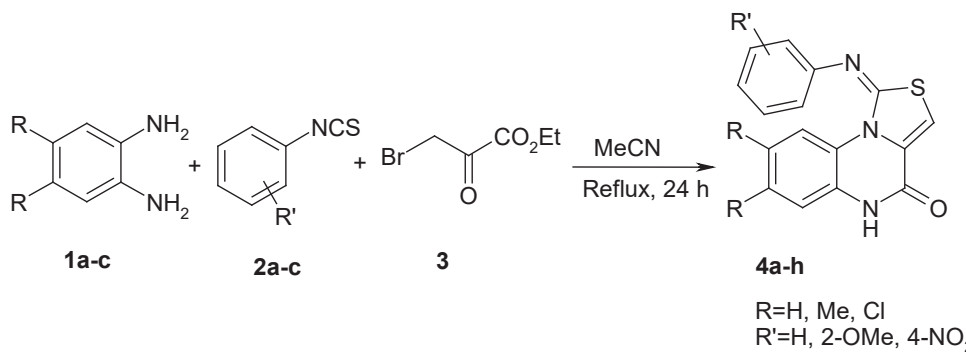
Reaction of benzene-1,2-diamine derivatives with aryl isothiocyanates in the presence of ethyl bromopyruvate in CH_3CN under reflux leads to the corresponding thiazolo[3,4-*a*] quinoxalines **4a**–**h** in 90–95% yields. To show the generality and scope of this new protocol, I used various 1,2-diamine derivatives and aryl isothiocyanates. The results are summarised in Fig. 1. The present protocol efficiently (high yield) and concisely (one-pot, compared with earlier reported protocols) furnishes various thiazolo[3,4-*a*]quinoxaline compounds.

The structures of compounds **4a**–**h** were deduced from their IR, ^{1}H NMR and ^{13}C NMR spectra. For example, the ^{1}H NMR spectrum of **4a** exhibited a broad singlet at 11.37 ppm due to the NH group, along with multiplets (7.02–9.36 ppm) for the aromatic region. The proton-decoupled ^{13}C NMR spectrum of **4a** exhibited 14 signals in agreement with the proposed structure.

A postulated mechanism for the reaction is shown in Scheme 2. Presumably, nucleophilic addition of 1,2-diaminobenzene **1a** to the isothiocyanate **2a** leads to the formation of product **5**, a thiourea derivative with one dominant nucleophilic (C=S) site. The highly polar C–Br bond of ethyl bromopyruvate **3** is activated towards the nucleophilic attack of sulfur, resulting in S-alkylation to give species **6**. The thiourea nitrogen then attacks the carbonyl group to produce **7** by elimination of H_2O; subsequent intermolecular cyclisation of the intermediate 7 leads to thiazolo[3,4-*a*]quinoxaline **4a**.

Conclusion

I have demonstrated an efficient, one-pot method for the synthesis of thiazolo[3,4-*a*]quinoxaline derivatives

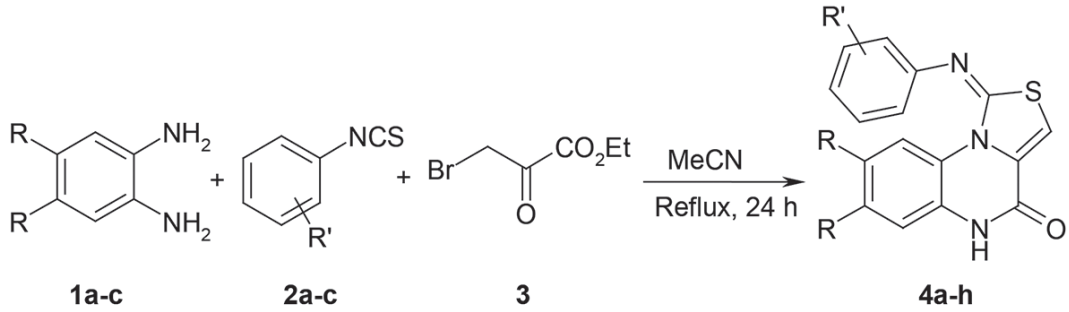


1a-c **2a-c** **3** **4a-h**

R=H, Me, Cl
R'=H, 2-OMe, 4-NO_2

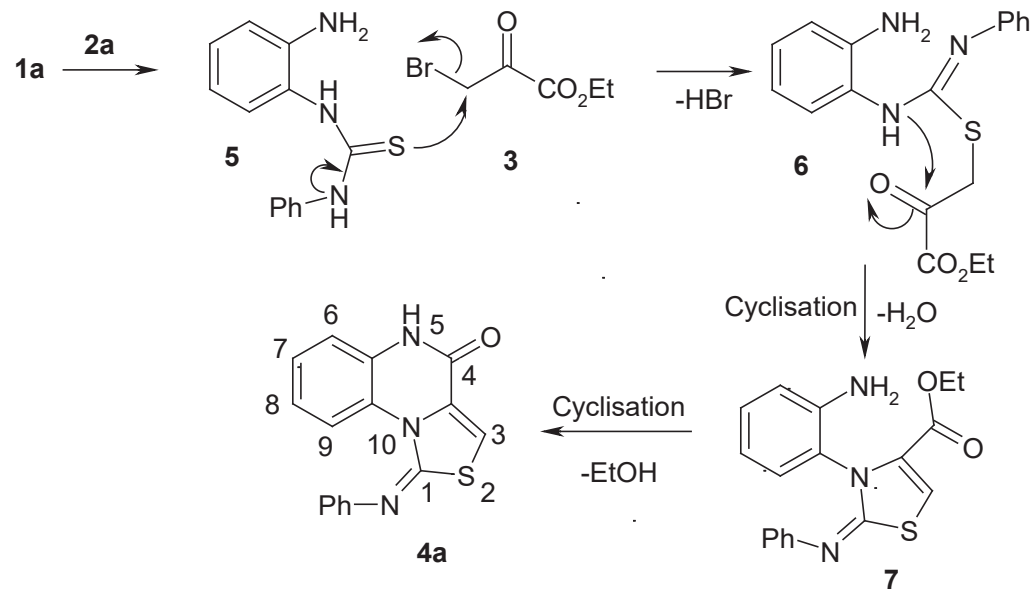
Scheme 1

* Correspondent. E-mail: mohammadpiltan@yahoo.com



4	R	R'	Yield (%)
a	H	H	**92**
b	H	2-MeO	**90**
c	H	4-NO_2	**92**
d	Me	H	**94**
e	Me	2-MeO	**90**
f	Me	4-NO_2	**95**
g	Cl	H	**90**
h	Cl	4-NO_2	**91**

Fig. 1 One-pot synthesis of thiazolo[3,4-*a*]quinoxaline derivatives



Scheme 2

from the simple starting materials benzene-1,2-diamines, aryl isothiocyanate and ethyl bromopyruvate to produce thiazolo[3,4-*a*]quinoxalines in good to excellent yields. The present method is attractive due to its facile conditions, suggesting that this protocol could be an alternative to other procedures. The products can be isolated very easily without the use of chromatography.

Experimental

Benzene-1,2-diamines, aryl isothiocyanate, ethyl bromopyruvate and all solvents were obtained from Merck or Fluka and used without further purification. Melting points were determined using an Electrothermal-9100 apparatus and are uncorrected. IR spectra were obtained using a Shimadzu IR-460 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were obtained on Bruker DRX-250 and 400 Avance instruments in DMSO-d_6 at 250, 400, 75 and 100 MHz, respectively. Elemental analyses were obtained using a Heraeus CHN-O-Rapid analyser.

Synthesis of **4**; *general procedure*

A mixture of the appropriate benzene-1,2-diamine **1** (1 mmol) and aryl isothiocyanate **2** (1 mmol) in MeCN (5 mL) was stirred for 20 min at room temperature, then ethyl bromopyruvate **3** (1 mmol) was added to the reaction mixture. The reaction mixture was refluxed for 24 h. After completion of the reaction, as indicated by TLC (AcOEt/hexane, 1:4), the reaction mixture was cooled, and the resulting precipitate was filtered off and washed with Et_2O (5 mL) to give the pure products **4a**–**h**.

*1-(Phenylimino)-3*H*-thiazolo[3,4-*a*]quinoxalin-4(5*H*)-one* (**4a**): Beige powder; yield 0.27 g (92%); m.p. >300 °C; FTIR (KBr) (υ_{max} cm^{-1}): 3184, 3118, 3085, 3025, 2982, 2853, 1685, 1624, 1590, 1575; ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.02 (d, 2H, *J* = 8.1 Hz, 2ArH), 7.11–7.18 (m, 3H, 3ArH), 7.27–7.31 (m, 2H, H3 and ArH), 7.40 (d, 2H, *J* = 7.5 Hz, 2ArH), 9.36 (d, 1H, *J* = 8.8 Hz, H9), 11.37 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 105.5, 115.5, 117.2, 120.6, 122.6, 123.7, 124.8, 125.1, 127.6, 128.6, 129.8, 150.7, 153.5, 156.8. Anal. calcd for $C_{16}H_{11}N_3OS$ (293.35): C, 65.51; H, 3.78; N, 14.32; found: C, 65.47; H, 3.71; N, 14.44%.

*1-(2-Methoxyphenylimino)-3*H*-thiazolo[3,4-*a*]quinoxalin-4(5*H*)-one* (**4b**): Beige powder; yield: 0.29 g (90%); m.p. >300 °C; FTIR (KBr) (υ_{max} cm^{-1}): 3175, 3115, 3084, 3020, 2985, 2854, 1684, 1624, 1590, 1573, 1461, 1429, 1282; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.76 (s, 3H, OCH_3), 6.95–7.01 (m, 3H, 3ArH), 7.10–7.17 (m, 3H, 3ArH), 7.29–7.34 (m, 2H, H3 and ArH), 9.43 (d, 1H, *J* = 8.4 Hz, H9), 11.40 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 56.3, 105.7, 117.1, 118.7, 121.9, 123.5, 124.0, 125.2, 125.8, 126.3, 128.2, 129.2, 129.9, 133.4, 151.7, 153.7, 155.0. Anal. calcd for $C_{17}H_{13}N_3O_2S$ (323.38): C, 63.14; H, 4.05; N, 12.99; found: C, 63.25; H, 4.11; N, 13.06%.

*1-(4-Nitrophenylimino)-3*H*-thiazolo[3,4-*a*]quinoxalin-4(5*H*)-one* (**4c**): Beige powder; yield: 0.31 g (92%); m.p. >300 °C; FTIR (KBr) (υ_{max} cm^{-1}): 3194, 3125, 3084, 3020, 2983, 2861, 1680, 1624, 1587, 1572, 1485, 1415, 1394; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.11–7.18 (m, 3H, 3ArH), 7.27 (s, 1H, H3), 7.48 (d, 2H, *J* = 8.8 Hz, 2ArH), 8.22 (d, 2H, *J* = 8.8 Hz, 2ArH), 9.40 (d, 1H, *J* = 8.4 Hz, H9), 11.64 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 105.4, 116.6, 120.4, 121.7, 122.7, 124.1, 125.2, 125.6, 126.0, 128.8, 129.7, 132.5, 150.0, 153.3, 154.5; Anal. calcd for $C_{16}H_{10}N_4O_3S$ (338.35): C, 65.80; H, 2.98; N, 16.56; found: C, 65.67; H, 3.04; N, 16.44%.

*7,8-Dimethyl-1-(phenylimino)-3*H*-thiazolo[3,4-*a*]quinoxalin-4(5*H*)-one* (**4d**): Beige powder; yield: 0.30 g (94%); m.p. >300 °C; FTIR (KBr) (υ_{max} cm^{-1}): 3178, 3116, 3098, 3045, 2980, 2855, 1687, 1622, 1587, 1571, 1431, 1417; ^{1}H NMR (250 MHz, DMSO-d_6): δ 2.17 (s, 6H, 2 CH_3), 6.87 (s, 1H, H6), 7.02 (d, 2H, *J* = 7.5 Hz, 2ArH), 7.11 (t, 1H, *J* = 7.6 Hz, ArH), 7.22 (s, 1H, H3), 7.39 (t, 2H, *J* = 7.5 Hz, 2ArH), 9.14 (s, 1H, H9), 11.21 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 19.4, 19.9, 105.7, 116.7, 118.4, 121.3, 123.1, 124.3, 125.8, 129.0, 130.4, 130.8, 133.5, 150.1, 151.4, 154.1. Anal. calcd for $C_{18}H_{15}N_3OS$ (321.40): C, 67.27; H, 4.70; N, 13.07; found: C, 67.42; H, 4.84; N, 13.14%.

*7,8-Dimethyl-1-(2-methoxyphenylimino)-3*H*-thiazolo[3,4-*a*]quinoxalin-4(5*H*)-one* (**4e**): Beige powder; yield: 0.32 g (90%); m.p. >300 °C; FTIR (KBr) (υ_{max} cm^{-1}): 3204, 3135, 3094, 2995, 2853, 1685, 1628, 1591, 1573, 1461, 1429, 1413, 1286, 756, 694; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.32 (s, 3H, $2CH_3$), 2.34 (s, 3H, $2CH_3$), 3.76 (s, 3H, OCH_3), 6.90 (s, 1H, H6), 7.01 (t, *J* = 7.6 Hz, ArH), 7.10 (d, *J* = 7.2 Hz, ArH), 7.12 (s, 1H, H3), 7.25 (d, *J* = 7.6 Hz, ArH), 7.32 (t, *J* = 7.6 Hz, ArH), 9.11 (s, 1H, H9), 11.21 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.5, 20.4, 56.2, 105.5, 116.7, 118.3, 121.2, 126.3, 126.7, 126.8, 128.5, 129.6, 130.0, 130.3, 130.6, 132.8, 150.1, 153.9, 154.6. Anal. calcd for $C_{19}H_{17}N_3O_2S$ (351.43): C, 64.94; H, 4.88; N, 11.96; found: C, 64.82; H, 4.81; N, 12.05%.

*7,8-Dimethyl-1-(4-nitrophenylimino)-3*H*-thiazolo[3,4-*a*]quinoxalin-4(5*H*)-one* (**4f**): Beige powder; yield: 0.32 g (95%); m.p. >300 °C; FTIR (KBr) (υ_{max} cm^{-1}): 3198, 3121, 3095, 2985, 2855, 1682, 1628, 1585, 1578, 1485, 1418; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.28 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 6.88 (s, 1H, H6), 7.16 (s, 1H, H3), 7.48 (d, 2H, *J* = 8.4 Hz, 2ArH), 8.26 (d, 2H, *J* = 8.4 Hz, 2ArH), 9.18 (s, 1H, H9), 11.31 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.3, 19.8, 105.8, 116.4, 119.7, 122.3, 125.5, 125.7, 126.5, 128.9, 129.6, 130.0, 132.4, 149.7, 151.6, 154.3. Anal. calcd for $C_{18}H_{14}N_4O_3S$ (336.40): C, 59.01; H, 3.85; N, 15.29; found: C, 59.11; H, 3.75; N, 15.14%.

*7,8-Dichloro-1-(phenylimino)-3*H*-thiazolo[3,4-*a*]quinoxalin-4(5*H*)-one* (**4g**): Beige powder; yield: 0.33 g (90%); m.p. >300 °C; FTIR (KBr) (υ_{max} cm^{-1}): 3218, 3121, 3094, 2993, 2854, 1686, 1627, 1584, 1575, 1487, 1396; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.91 (s, 1H, H6), 7.07 (d, 2H, *J* = 7.2 Hz, 2ArH), 7.17 (t, 1H, *J* = 7.2 Hz, ArH), 7.36 (s, 1H, H3), 7.44 (d, 2H, *J* = 7.6 Hz, 2ArH), 9.61 (s, 1H, H9), 11.61 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 105.9, 117.4, 119.9, 121.7, 121.3, 126.6, 127.3, 128.1, 128.9, 130.6, 132.5, 154.3, 156.9, 160.7. Anal. calcd for $C_{16}H_9Cl_2N_3OS$ (362.24): C, 53.05; H, 2.50; N, 11.60; found: C, 53.12; H, 2.58; N, 11.51%.

*7,8-Dichloro-1-(4-nitrophenylimino)-3*H*-thiazolo[3,4-*a*]quinoxalin-4(5*H*)-one* (**4h**): Beige powder; yield: 0.37 g (91%); m.p. >300 °C; FTIR (KBr) (υ_{max} cm^{-1}): 3245, 3131, 3084, 3020, 2983, 2923, 2853, 1684, 1627, 1585, 1572, 1485, 1413, 1394; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.90 (s, 1H, H6), 7.34 (s, 1H, H3), 7.43 (d, 2H, *J* = 8.8 Hz, 2ArH), 8.21 (d, 2H, *J* = 9.2 Hz, 2ArH), 9.55 (s, 1H, H9), 11.39 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 106.4, 116.4, 119.7, 122.3, 125.7, 126.0, 126.5, 128.9, 129.6, 129.9, 132.4, 150.0, 152.6, 154.0. Anal. calcd for $C_{16}H_8Cl_2N_4O_3S$ (407.24): C, 47.19; H, 1.98; N, 13.76; found: C, 47.28; H, 1.91; N, 13.84%.

Acknowledgements

The author gratefully acknowledges the Research Council of the Islamic Azad University of Sanandaj Branch for financial support of this project.

Electronic Supplementary Information

Copies of the ^{1}H and ^{13}C NMR spectra for all new compounds are available through: http://ingentaconnect.com/content/stl/jcr/2017/00000041/00000012/art00009

Received 7 September 2017; accepted 6 December 2017
Paper 1704985
https://doi.org/10.3184/174751917X15127369231305
Published online: 15 December 2017

References

1 M.N. Nasr, *Arch. Pharm. Med. Chem.*, 2002, **8**, 389.
2 Y. Jinbo, H. Kondo, M. Tagichi, F. Sakamoto and G. Tsukamoto, *J. Org. Chem.*, 1994, **59**, 6057.
3 M. Negwer and H.G. Scharnow, *Organic chemical drugs and their synonyms*. Wiley-VCH, Weinheim, 2001, Vols 2 and 3.
4 E.A. Adegoke and B.J. Alo, *J. Heterocycl. Chem.*, 1983, **20**, 1513.
5 M. Benchidmi, E.M. Essassi, S. Ferfra and J. Fifani, *Bull. Soc. Chim. Belg.*, 1993, **102**, 679.
6 A.A. Kalinin, O.G. Isaikina and V.A. Mamedov, *Chem. Heterocycl. Compd*, 2004, **40**, 1510.
7 A.A. Kalinin and V.A. Mamedov, *Chem. Heterocycl. Compd*, 2004, **40**, 129.
8 V.A. Mamedov, N.A. Zhukova, A.A. Balandina, S.V. Kharlamov, T.N. Beschastnova, I.K. Rizvanov and S.K. Latypov, *Tetrahedron*, 2012, **68**, 7363.
9 Z. Sharafi and M. Piltan, *Heterocycl. Commun.*, 2016, **22**, 53.
10 M. Piltan, *J. Chem. Res.*, 2016, **40**, 410
11 L. Moradi, M. Piltan and G. Abasi, *Helv. Chim. Acta*, 2014, **97**, 646.
12 L. Moradi, M. Piltan, H. Rostami and G. Abasi, *Chin. Chem. Lett.*, 2013, **24**, 740.
13 M. Piltan, *Chin. Chem. Lett.*, 2014, **25**, 1507.