Reaction of aryl isothiocyanate with pyridines and dialkyl acetylenedicarboxylates to afford novel heterocycles

Alireza Hassanabadi[a]* and Rahele Zhiani[b]

[a]*Department of Chemistry, Zahedan Branch, Islamic Azad University, PO Box 98135-978, Zahedan, Iran*

[b]*Department of Chemistry, Neyshabur Branch, Islamic Azad University, Neyshabur, Iran*

The reactive intermediate produced in the reaction between pyridines and dialkyl acetylenedicarboxylates was trapped by aryl isothiocyanates to afford 2-thioxo-1,9a-dihydro-2*H*-pyrido [1,2,*a*]pyrimidine derivatives in good yields.

Keywords: three-component reaction, dialkyl acetylenedicarboxylates, pyridines, aryl isothiocyanates

Multi-component reactions (MCRs) are powerful tools in modern drug discovery processes and allow fast, automated and high throughput generation of organic compounds.[1,2] Bridgehead nitrogen heterocycles are of interest because they constitute an important class of natural and unnatural products, many of which exhibit useful biological activity.[3,4] The interest in bicyclic 6–6 systems with one ring junction and one extra nitrogen atom, stems from the appearance of saturated and partially saturated pyrido[1,2-*a*]pyrimidine ring systems in many biologically active compounds and natural products,[4–10] some of which are key intermediates for the synthesis of rutaecarpine alkaloids. Some have characteristic pharmacological properties such as analgesic anti-allergic, anti-asthmatic and anti-psychotic agents, and some are neutral hydrogen chloride acceptors in organic synthesis.[4]

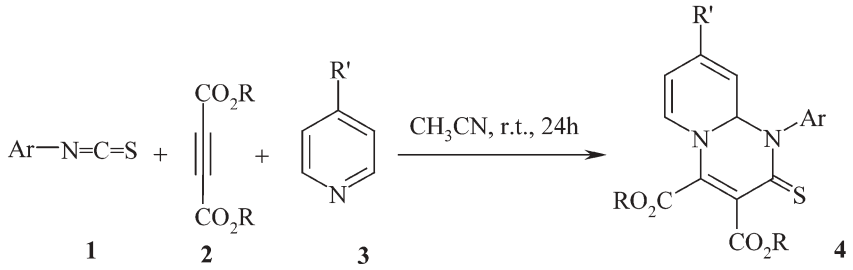
As part of an ongoing development of efficient protocols for the preparation of biologically active heterocycles,[11,12] we report here the results of our study on the reaction between aryl isothiocyanates and dialkyl acetylenedicarboxylates in the presence of pyridines.

Results and discussion

The reaction of aryl isothiocyanates **1** with dialkyl acetylenedicarboxylates **2** in the presence of pyridines **3** produces 2-thioxo-1,9a-dihydro-2*H*-pyrido [1,2,*a*]pyrimidine derivatives **4a–g** in excellent yields (Scheme 1).

The structures of compounds **4a–g** were deduced from their elemental analyses and their IR, ^{1}H NMR, ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at appropriate *m/z* values.

The ^{1}H NMR spectrum of compound **4a** exhibited two single sharp lines readily recognised as arising from methoxy protons (3.78 and 3.96) along with four multiplets for the protons of an electron rich diene and an allylic proton as well as characteristic multiplets for the aromatic protons. The ^{13}C NMR spectrum of compound **4a** showed 16 distinct signals in agreement with the proposed structure. The ^{13}C NMR spectrum of **4a** showed the thiocarbonyl resonance at δ = 194.08 ppm. The mass spectrum of **4a** displayed the molecular ion peak at *m/z* = 356. The IR spectrum of compound **4a** also supported the suggested structure.



1	Ar
a	C_6H_5
b	4-$CH_3C_6H_4$

2	R
a	CH_3
b	C_2H_5

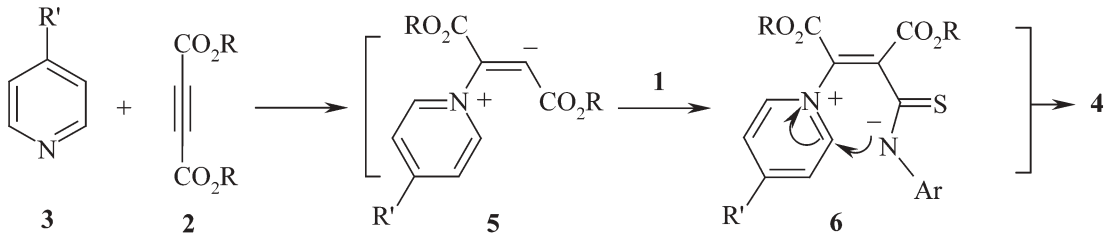
3	R'
a	H
b	CH_3

4	Ar	R'	R	%Yield *
a	C_6H_5	H	CH_3	90
b	C_6H_5	H	C_2H_5	87
c	C_6H_5	CH_3	CH_3	88
d	C_6H_5	CH_3	C_2H_5	82
e	4-$CH_3C_6H_4$	H	CH_3	91
f	4-$CH_3C_6H_4$	H	C_2H_5	88
g	4-$CH_3C_6H_4$	CH_3	CH_3	85

* Isolated yields

Scheme 1 Reaction of aryl isothiocyanate and dialkyl acetylenedicarboxylates in the presence of pyridines.

* Correspondent. Email: ar_hasanabadi@yahoo.com



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

The formation of compounds **4** can be rationalised as shown in Scheme 2. The first step may involve addition of the pyridine to the dialkyl acetylenedicarboxylateand formation of the 1:1 adduct **5**. Subsequent nucleophilic attack of the adduct to the aryl isothiocyanate would yield anion **6**. The observed product is formed from the intramolecular addition of the nitrogen to the pyridinium moiety.

In summary, we have observed a three-component condensation reaction that offers an easy and effective one-pot synthesis of 2-thioxo-1,9a-dihydro-2*H*-pyrido [1,2,*a*]pyrimidine derivatives. The present method has the advantage that the reaction is performed under neutral conditions and the substances can be mixed without any activation or modification.

Experimental

Melting points were determined with an Electrothermal 9100 apparatus and 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 NMR spectra were recorded on Bruker DRX-500 Avance spectrometer at solution in $CDCl_3$ using TMS as internal standard. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

General procedure

A mixture of dialkyl acetylenedicarboxylate (1 mmol) in acetonitrile (3 mL) via a syringe was added dropwise to a magnetically stirred solution of aryl isothiocyanate (1 mmol) and pyridine in acetonitrile (15 mL) at –5 °C over 10 min. The reaction mixture was then stirred for 24 h at room temperature. 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 and the resulting precipitate washed with cold diethyl ether (10 mL) to afford the product.

Dimethyl-1-phenyl-2-thioxo-1,9a-dihydro-2H-pyrido[1,2,a]pyrimidine-3,4-dicarboxylate (**4a**): Yellow powder; yield 90%; m.p. 111–113 °C, IR (KBr) (ν_{max}/cm^{-1}): 1734, 1648, 1358 and 1264. Anal.Calcd for $C_{18}H_{16}N_2O_4S$, C, 60.66; H, 4.53; N, 7.86. Found: C, 60.50; H, 4.60; N, 7.94%. MS (*m/z*, %): 356 (10). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.78 and 3.96 (6H, 2s, $2OCH_3$), 5.17 (1H, dd, *J* = 10.1 Hz and *J* = 3.1 Hz, CH), 5.36 (1H, dd, *J* = 6.9 Hz and *J* = 7.6 Hz, CH), 6.03 (1H, dd, *J* = 8.3 Hz and *J* = 7.9 Hz, CH), 6.18 (1H, dd, *J* = 3.1 Hz and *J* = 1.9 Hz, N–CH–N), 6.47 (1H, d, *J* = 7.6 Hz, N–CH=CH), 7.16 (2H, d, *J* = 7.5 Hz, *ortho* CH), 7.26 (1H, dt, *J* = 2.4 Hz and *J* = 7.1 Hz, *para* CH), 7.36 (2H, t, *J* = 7.0 Hz, *meta* CH) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 52.37 and 53.64 ($2OCH_3$), 69.42 (N-CH-N), 104.34, 105.12, 115.79, 123.44, 123.78, 127.82, 128.60, 129.61, 134.72 and 149.24 (aromatic and olefinic), 162.96 and 164.80 (2C=O), 194.08 (C=S) ppm.

Diethyl-1-phenyl-2-thioxo-1,9a-dihydro-2H-pyrido[1,2,a]pyrimidine-3,4-dicarboxylate (**4b**): Yellow powder; yield 87%; m.p. 101–103 °C, IR (KBr) (ν_{max}/cm^{-1}): 1736, 1645, 1351 and 1262. Anal.Calcd for $C_{20}H_{20}N_2O_4S$, C, 62.48; H, 5.24; N, 7.29. Found: C, 62.55; H, 5.30; N, 7.41%. MS (*m/z*, %): 384 (5). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.16 and 1.35 (6H, 2t, *J* = 7.1 Hz, $2CH_3$), 4.12–4.34 (4H, m, $2OCH_2$), 5.15 (1H, dd, *J* = 10.1 Hz and *J* = 3.1 Hz, CH), 5.33 (1H, dd, *J* = 6.9 Hz and *J* = 7.6 Hz, CH), 6.07 (1H, dd, *J* = 8.3 Hz and *J* = 7.9 Hz, CH), 6.24 (1H, dd, *J* = 3.1 Hz and *J* = 1.9 Hz, N–CH–N), 6.45 (1H, d, *J* = 7.6 Hz, N–CH=CH), 7.18 (2H, d, *J* = 7.5 Hz, *ortho* CH), 7.31 (1H, dt, *J* = 2.4 Hz and *J* = 7.1 Hz, *para* CH), 7.38 (2H, t, *J* = 7.0 Hz, *meta* CH) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.81, 14.27 ($2CH_3$), 62.56, 62.77 ($2OCH_2$), 69.37 (N-CH-N), 104.28, 105.19, 115.71, 123.52, 123.85, 127.74, 128.68, 129.52, 134.63 and 149.37 (aromatic and olefinic), 163.04 and 164.76 (2C=O), 194.02 (C=S) ppm.

Dimethyl-8-methyl-1-phenyl-2-thioxo-1,9a-dihydro-2H-pyrido[1,2,a]-pyrimidine-3,4-dicarboxylate (**4c**): Yellow powder; yield 88%; m.p. 124–126 °C, IR (KBr) (ν_{max}/cm^{-1}): 1735, 1643, 1350 and 1268. Anal. Calcd for $C_{19}H_{18}N_2O_4S$, C, 61.61; H, 4.90; N, 7.56. Found: C, 61.65; H, 4.86; N, 7.50%. MS (*m/z*, %): 370 (7).^{1}H NMR (500 MHz, $CDCl_3$): δ 2.23 (3H, s, CH_3), 3.73 and 3.92 (6H, 2s, $2OCH_3$), 5.21 (1H, d, *J* = 3.1 Hz, CH), 5.35 (1H, d, *J* = 7.6 Hz, CH), 6.22 (1H, d, *J* = 3.1 Hz, N–CH–N), 6.45 (1H, d, *J* = 7.6 Hz, N–CH=CH), 7.11 (2H, d, *J* = 7.5 Hz, *ortho* CH), 7.19 (1H, dt, *J* = 2.4 Hz and *J* = 7.1 Hz, *para* CH), 7.42 (2H, t, *J* = 7.0 Hz, *meta* CH) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 18.54 (CH_3), 52.31 and 53.60 ($2OCH_3$), 69.55 (N-CH-N), 104.46, 105.27, 115.62, 123.30, 123.89, 127.75, 128.72, 129.50, 134.59 and 149.43 (aromatic and olefinic), 162.88 and 164.73 (2C=O), 193.85 (C=S) ppm.

Diethyl-8-methyl-1-phenyl-2-thioxo-1,9a-dihydro-2H-pyrido[1,2,a]-pyrimidine-3,4-dicarboxylate (**4d**): Yellow powder; yield 82%; m.p. 107–109 °C, IR (KBr) (ν_{max}/cm^{-1}): 1740, 1652, 1353 and 1266. Anal. Calcd for $C_{21}H_{22}N_2O_4S$, C, 63.30; H, 5.56; N, 7.03. Found: C, 63.27; H, 5.44; N, 7.10%. MS (*m/z*, %): 398 (4). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.22 and 1.36 (6H, 2t, *J* = 7.1 Hz, $2CH_3$), 2.20 (3H, s, CH_3), 4.17–4.38 (4H, m, $2OCH_2$), 5.10 (1H, d, *J* = 3.1 Hz, CH), 5.41 (1H, d, *J* = 7.6 Hz, CH), 6.33 (1H, d, *J* = 3.1 Hz, N–CH–N), 6.44 (1H, d, *J* = 7.6 Hz, N–CH=CH), 7.23 (2H, d, *J* = 7.5 Hz, *ortho* CH), 7.25 (1H, dt, *J* = 2.4 Hz and *J* = 7.1 Hz, *para* CH), 7.39 (2H, t, *J* = 7.0 Hz, *meta* CH) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.74, 14.25 ($2CH_3$), 18.51 (CH_3), 62.53, 62.74 ($2OCH_2$), 69.42 (N-CH-N), 104.15, 105.22, 115.61, 123.50, 123.84, 127.63, 128.70, 129.55, 134.60 and 149.34 (aromatic and olefinic), 163.00 and 164.71 (2C=O), 193.90 (C=S) ppm.

Dimethyl-2-thioxo-1-ρ-tolyl-1,9a-dihydro-2H-pyrido[1,2,a]pyrimidine-3,4-dicarboxylate (**4e**): Yellow powder; yield 91%; m.p. 134–136 °C, IR (KBr) (ν_{max}/cm^{-1}): 1732, 1645, 1352 and 1261. Anal.Calcd for $C_{19}H_{18}N_2O_4S$, C, 61.61; H, 4.90; N, 7.56. Found: C, 60.75; H, 4.83; N, 7.60%. MS (*m/z*, %): 370 (4). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.41 (3H, s, CH_3), 3.72 and 3.98 (6H, 2s, $2OCH_3$), 5.25 (1H, dd, *J* = 10.1 Hz and *J* = 3.1 Hz, CH), 5.32 (1H, dd, *J* = 6.9 Hz and *J* = 7.6 Hz, CH), 6.08 (1H, dd, *J* = 8.3 Hz and *J* = 7.9 Hz, CH), 6.14 (1H, dd, *J* = 3.1 Hz and *J* = 1.9 Hz, N–CH–N), 6.49 (1H, d, *J* = 7.6 Hz, N–CH=CH), 7.21 (2H, d, *J* = 7.8 Hz, aromatic), 7.50 (2H, d, *J* = 7.8 Hz, aromatic) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 21.44 (CH_3), 52.45 and 53.58 ($2OCH_3$), 68.95 (N–CH–N), 103.88, 105.26, 114.92, 123.59, 123.67, 128.35, 128.84, 129.97, 134.82 and 149.40 (aromatic and olefinic), 162.85 and 164.67 (2C=O), 193.53 (C=S) ppm.

Diethyl-2-thioxo-1-ρ-tolyl-1,9a-dihydro-2H-pyrido[1,2,a]pyrimidine-3,4-dicarboxylate (**4f**): Yellow powder; yield 88%; m.p. 116–118 °C, IR (KBr) (ν_{max}/cm^{-1}): 1737, 1643, 1354 and 1265. Anal.Calcd for $C_{21}H_{22}N_2O_4S$, C, 63.30; H, 5.56; N, 7.03. Found: C, 63.26; H, 5.65; N, 7.10%. MS (*m/z*, %): 398 (7). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.22 and 1.34 (6H, 2t, *J* = 7.1 Hz, $2CH_3$), 2.35 (3H, s, CH_3), 4.10–4.47 (4H, m, $2OCH_2$), 5.11 (1H, dd, *J* = 10.1 Hz and *J* = 3.1 Hz, CH), 5.38 (1H, dd, *J* = 6.9 Hz and *J* = 7.6 Hz, CH), 6.15 (1H, dd, *J* = 8.3 Hz and *J* = 7.9 Hz, CH), 6.30 (1H, dd, *J* = 3.1 Hz and *J* = 1.9 Hz, N–CH–N), 6.46 (1H, d, *J* = 7.6 Hz, N–CH=CH), 7.26 (2H, d, *J* = 7.8 Hz, aromatic), 7.52 (2H, d, *J* = 7.8 Hz, aromatic) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.94, 14.25 ($2CH_3$), 21.52 (CH_3), 62.51, 62.80 ($2OCH_2$),

69.42 (N-CH-N), 104.25, 105.13, 114.70, 123.75, 123.94, 128.36, 128.72, 130.06, 134.51 and 149.32 (aromatic and olefinic), 163.12 and 164.80 (2C=O), 194.15 (C=S) ppm.

Dimethyl-8-methyl-2-thioxo-1-ρ-tolyl-1,9a-dihydro-2H-pyrido[1,2,a]-pyrimidine-3,4-dicarboxylate (**4g**): Yellow powder; yield 85%; m.p. 135–137 °C, IR (KBr) (ν_{max}/cm^{-1}): 1736, 1640, 1355 and 1264. Anal. Calcd for $C_{20}H_{20}N_2O_4S$, C, 62.48; H, 5.24; N, 7.29. Found: C, 62.40; H, 5.30; N, 7.40%. MS (*m/z*, %): 384 (10).^{1}H NMR (500 MHz, $CDCl_3$): δ 2.17 (3H, s, CH_3), 2.32 (3H, s, CH_3), 3.80 and 3.93 (6H, 2s, $2OCH_3$), 5.16 (1H, d, *J* = 3.1 Hz, CH), 5.38 (1H, d, *J* = 7.6 Hz, CH), 6.12 (1H, d, *J* = 3.1 Hz, N–CH–N), 6.40 (1H, d, *J* = 7.6 Hz, N–CH=CH), 7.24 (2H, d, *J* = 7.8 Hz, aromatic), 7.57 (2H, d, *J* = 7.8 Hz, aromatic) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 18.62 (CH_3), 21.38 (CH_3), 52.34 and 53.66 ($2OCH_3$), 69.48 (N-CH-N), 104.33, 105.16, 113.87, 123.35, 124.08, 128.27, 128.84, 129.90, 134.46 and 149.27 (aromatic and olefinic), 162.94 and 164.81 (2C=O), 193.92 (C=S) ppm.

Received 21 April 2013; accepted 20 May 2014
Paper 1301904 doi: 10.3184/174751913X13726957255037
Published online: 9 August 2013

References

1 L. Weber, *Curr. Med. Chem.*, 2002, **9**, 1241.
2 R.W. Armstrong, A.P. Combs, P.A. Tempest, S.D. Brown and T.A. Keating, *Acc. Chem. Res*., 1996, **29**, 123.
3 J.F. Swinbourne, H.J. Hunt and G. Klinkert, *Adv. Heterocycl. Chem.*, 1987, **23**, 103.
4 I. Hermecz, L. Vasvari-Debreczy and P. Matyus, *Comprehensive heterocyclic chemistry*, A.R. Katritzky, C.W. Rees and E.V.F. Scriven, eds. Pergamon, London, 1996; Chap. 8.23, pp. 563–595.
5 F.C. Colpaert, *Nat. Rev. Drug Discovery*, 2003, **2**, 315.
6 G. Leoncini, M.G. Signorello, G. Roma and M. Di Braccio, *Biochem. Pharmacol.*, 1997, **53**, 1667.
7 V.S. Bogdanov, K.L. Cherkasova, V.A. Dorokhov, O.V. Shishkin and Y.T. Struchkov, *Mendeleev Commun.*, 1995, **5**, 106.
8 M. Gullu, S. Uzun and S. Yalcin, *Tetrahedron Lett.*, 2003, **44**, 1939.
9 B. Djerrari, E.M. Essassi, J. Fifani and B. Garrigues, *C.R. Chim.*, 2002, **5**, 177.
10 J.M. Mellor, G.D. Merriman, H. Rataj and G. Reid, *Tetrahedron Lett.*, 1996, **37**, 2615.
11 A. Hassanabadi, M.H. Mosslemin and S.E. Tadayonfar, *J. Chem. Res*., 2011, **35**, 29.
12 A. Hassanabadi, M.H. Mosslemin, M. Anary-Abbasinejad, M.R. Hosseini-Tabatabaei, H. Mahmoudian and S.E. Tadayonfar, *J. Sulfur. Chem*., 2011, **32**, 355.