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One-pot synthesis of pyrrolo[1,2-*a*]pyrazines *via* three component reaction of ethylenediamine, acetylenic esters and nitrostyrene derivatives

Loghman Moradi [a,*], Mohammad Piltan [b], Hedieh Rostami [a], Golaleh Abasi [a]

[a] Department of Chemistry, Faculty of Science, University of Kurdistan, P.O. Box 416, Sanandaj, Iran
[b] Young Researches Club, Sanandaj Branch, Islamic Azad University, Sanandaj, Iran

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ABSTRACT

An effective route to pyrrolo[1,2-*a*]pyrazines is described *via* reaction of ethylenediamine, acetylenic esters and nitrostyrene derivatives in the presence of 20 mol% of sulfamic acid.

1. Introduction

One of the main challenges in medicinal chemistry is the design and synthesis of biologically active molecules. Multi-component reactions (MCRs), because of their productivity, simple procedures, convergence, facile execution, and atomeconomy, are one of the best tools in the synthesis of diverse and complex compounds as well as small and drug like heterocycles [1–3]. Sulfamic acid (H_2NSO_3H, SA), a common inorganic acid, is nonvolatile, noncorrosive, stable, water resistance and incapable of forming complexes, making it an outstanding alternative to metal catalysts, in different areas of organic synthesis, as an efficient and green reagent [4–6]. In recent years, pharmacological evaluation and structure–activity relationships of some of pyrrolo[1,2-*a*]pyrazines have been reported [7,8].

As part of our study on the development of new routes to heterocyclic and carbocyclic systems [9–13], we now report a simple one-pot synthesis of functionalized pyrrolo[1,2-*a*]pyrazines **3**. Thus, reaction of ethylenediamine, acetylenic esters **1** and *β*-nitro styrene derivatives **2** in the presence of sulfamic acid (SA) leads to the corresponding functionalized pyrrolo[1,2-*a*]pyrazines **3a–3h** (Scheme 1).

2. Experimental

The reagents and solvents used in this work were obtained from Merck and were used without further purification. Mp: Electrothermal-9100 apparatus; uncorrected. IR spectra: Shimadzu IR-460 spectrometer; in cm^{-1}. ^1H NMR and ^{13}C NMR spectra: Bruker DRX-250.1 AVANCE instrument; in DMSO-d_6 at 250.1 MHz and 62.9 MHz, respectively; δ in ppm, J in Hz. EI-MS: Agilent-5975 C inert XL MSD mass spectrometer, at 70 eV; in m/z. Elemental analyses: Heraeus CHN-O-Rapid analyzer.

General procedure for the synthesis of compounds **3**: In a round bottom flask equipped with a magnetic stirrer, diethyl acetylenedicarboxylate (1.0 mmol) and ethylenediamine (1.2 mmol) in CH_3CN (3 mL) were charged and the mixture was stirred vigorously at room temperature. Then, *β*-nitrostyrene (1.0 mmol) and SA (20 mol%) were added to the mixture and then refluxed for 24 h. Upon completion, the reaction mixture was cooled to room temperature and then poured into 3 mL water. The solid product was removed by filtration and purified by recrystallization from 95% ethanol to afford the pure title compounds.

Methyl 1-oxo-7-phenyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-8-carboxylate (***3a***): Gray crystals; 0.24 g, 88%, mp 182–185 °C. IR (KBr, cm^{-1}): ν_{max} 3215 (NH broad), 1712 (C=O), 1655 (C=O), 1555, 1405, 1462. ^1H NMR (250 MHz, $CDCl_3$): δ 3.44 (t, 2H, $^3J_{HH}$ = 3.5 Hz, CH_2), 3.51 (t, 2H, $^3J_{HH}$ = 3.5 Hz, CH_2), 3.69 (s, 3H, OCH_3), 6.59–7.26 (m, 6H, 6H), 8.28 (s, 1H, NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 40.1 (CH_2), 44.3 (CH_2), 52.4 (OCH_3), 118.8 (N–CH=C), 120.8 (C), 123.1 (C), 125.4 (CH of Ar), 126.9 (C of Ar), 127.4 (2CH of Ar), 128.5 (2CH

* Corresponding author.
E-mail address: l.moradi@uok.ac.ir (L. Moradi).

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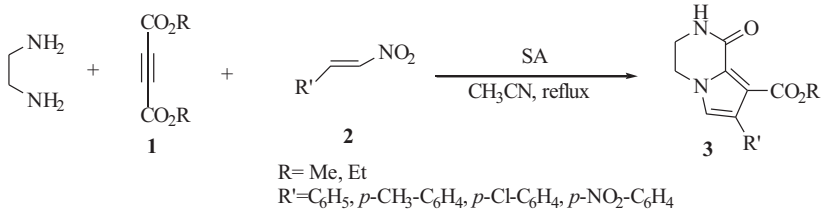


Scheme 1. Synthesis of pyrrolo[1,2-*a*]pyrazines.

of Ar), 133.4 (N–CH=C) 161.0 (C=O), 170.9 (C=O). Anal. calcd. for $C_{15}H_{14}N_2O_3$ (270.29); C, 66.66; H, 5.22; N, 10.36%; Found: C, 66.58; H, 5.19; N, 10.48.

Ethyl 1-oxo-7-p-tolyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-8-carboxylate (***3b***): Gray crystals, yield 0.27 g (90%), mp 186–190 °C (decomp). IR (KBr, cm^{-1}): ν_{max} 3305 (NH broad), 1714 (C=O), 1653 (C=O), 1604, 1552, 1495. ^1H NMR (250 MHz, $CDCl_3$): δ 1.44 (t, 3H, $^3J_{HH}$ = 7.2 Hz, CH_3), 2.34 (s, 3H, CH_3),3.48 (t, 2H, $^3J_{HH}$ = 3.5 Hz, CH_2), 3.46 (t, 2H, $^3J_{HH}$ = 3.5 Hz, CH_2), 4.29 (q, 2H, $^3J_{HH}$ = 7.2 Hz, CH_2), 6.59–7.26 (m, 5H, 5H), 8.26 (s, 1H, NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.1 (CH_3), 22.3 (CH_3), 40.2 (CH_2), 45.3 (CH_2), 62.4 (OCH_2), 117.7 (N–CH=C), 121.8 (C), 122.8 (C of Ar), 125.1 (C of Ar), 128.6 (2CH of Ph), 129.8 (2CH of Ph), 131.2 (C), 131.8 (N–CH=C), 158.7 (C=O), 165.3 (C=O). MS: *m*/*z* (%) 298 (M^+, 98), 269 (10), 253(100), 239(12), 226(30). Anal. calcd. for $C_{17}H_{18}N_2O_3$ (298.34) C, 68.44; H, 6.08; N, 9.39%; Found: C, 68.36; H, 5.87; N, 10.12.

Methyl 1-oxo-7-p-tolyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-8-carboxylate (***3c***): Gray crystals, yield 0.27 g (95%), mp 190–192 °C (decomp.). IR (KBr, cm^{-1}): ν_{max} 3304 (NH broad), 1713 (C=O), 1651 (C=O), 1600, 1553, 1499. ^1H NMR (250 MHz, $CDCl_3$): δ 2.30 (s, 3H, CH_3), 3.48 (t, 2H, $^3J_{HH}$ = 3.5 Hz, CH_2), 3.46 (t, 2H, $^3J_{HH}$ = 3.5 Hz, CH_2), 3.80 (s, 3H, OCH_3), 6.59–7.26 (m, 5H, 5H), 8.26 (s, 1H, NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 22.3 (CH_3), 40.2 (CH_2), 45.3 (CH_2), 52.4 (OCH_3), 117.7 (N–CH=C), 121.8 (C), 122.8 (C of Ar), 125.1 (C of Ar), 128.6 (2CH of Ph), 129.8 (2CH of Ph), 131.2 (C), 131.8 (N–CH=C), 158.7 (C=O), 165.3 (C=O). Anal. calcd. for $C_{16}H_{16}N_2O_3$ (284.32) C, 67.59; H, 5.67; N, 9.85%; Found: C, 67.50; H, 5.87; N, 9.92.

Ethyl 7-(4-cholorophenyl)-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-8-carboxylate (***3d***): Gray crystals; 0.28 g (88%), mp 183–185 °C (decomp). IR (KBr, cm^{-1}): ν_{max} 3212 (NH broad), 1718 (C=O), 1650 (C=O), 1560, 1526, 1419. ^1H NMR (250 MHz, $CDCl_3$): δ 1.20 (t, 3H, $^3J_{HH}$ = 7.1 Hz, CH_3), 3.72 (t, 2H, $^3J_{HH}$ = 4.0 Hz, CH_2), 4.14 (t, 2H, $^3J_{HH}$ = 4.0 Hz, CH_2), 4.21 (q, 2H, $^3J_{HH}$ = 7.1 Hz, CH_2), 7.20–7.32 (m, 5H, 5H), 8.70 (s, 1H, NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.1 (CH_3), 41.1 (CH_2), 45.2 (CH_2), 62.4 (OCH_2), 118.7 (N–CH=C), 120.7 (C), 123.2 (C of Ar), 123.3 (C of Ar), 127.6 (2CH of Ph), 128.9 (2CH of Ph), 130.9 (C), 132.6 (N–CH=C), 158.4 (C=O), 166.1 (C=O). Anal. calcd. for $C_{16}H_{15}ClN_2O_3$ (318.76) C, 60.25; H, 4.74; N, 8.79%; Found: C, 60.40; H, 4.23; N, 8.52.

Methyl 7-(4-cholorophenyl)-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-8-carboxylate (***3e***): Gray crystals; 0.27 g (89%), mp 193–195 °C (decomp). IR (KBr, cm^{-1}): ν_{max} 3210 (NH broad), 1720 (C=O), 1654 (C=O), 1568, 1529, 1429. ^1H NMR (250 MHz, $CDCl_3$): δ 3.70 (t, 2H, $^3J_{HH}$ = 4.0 Hz, CH_2), 3.84 (s, 3H, OCH_3), 4.11 (t, 2H, $^3J_{HH}$ = 4.0 Hz, CH_2), 6.69 (s, 1H, CH), 6.83 (s, 1H, NH), 7.22–7.31 (m, 4H, 4H of Ph). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 40.1 (CH_2), 44.3 (CH_2), 52.4 (OCH_3), 118.7 (N–CH=C), 120.8 (C), 123.3 (C of Ar), 124.3 (C of Ar), 128.7 (2CH of Ph), 128.8 (2CH of Ph), 131.9 (C), 132.8 (N–CH=C), 159.4 (C=O), 166.4 (C=O). Anal. calcd. for $C_{15}H_{13}ClN_2O_3$ (304.74) C, 59.12; H, 4.30; N, 9.19%; Found: C, 59.10; H, 4.23; N, 9.22.

Ethyl 1-oxo-7-phenyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-8-carboxylate (***3f***): Gray crystals; 0.24 g, 87%, mp 180–182 °C. IR (KBr, cm^{-1}): ν_{max} 3215 (NH broad), 1711 (C=O), 1653 (C=O), 1555, 1402, 1460. ^1H NMR (250 MHz, $CDCl_3$): δ 1.41 (t, 3H, $^3J_{HH}$ = 7.2 Hz, CH_3), 3.42 (t, 2H, $^3J_{HH}$ = 3.5 Hz, CH_2), 3.50 (t, 2H, $^3J_{HH}$ = 3.5 Hz, CH_2), 4.28 (q, 2H, $^3J_{HH}$ = 7.2 Hz, CH_2), 6.56–7.24 (m, 6H, 6H), 8.26 (s, 1H, NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.2 (CH_3), 40.2 (CH_2), 44.4 (CH_2), 62.3 (OCH_2), 118.4 (N–CH=C), 120.8 (C), 123.1 (C), 125.4 (CH of Ar), 126.7 (C of Ar), 127.2 (2CH of Ar), 128.7 (2CH of Ar), 133.3 (N–CH=C) 161.1 (C=O), 170.8 (C=O). Anal. calcd. For $C_{16}H_{16}N_2O_3$ (284.32) C, 67.59; H, 5.67; N, 9.85%; Found: C, 67.58; H, 5.79; N, 9.74.

Ethyl 7-(4-nitrophenyl)-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-8-carboxylate (***3g***): Gray crystals; 0.26 g (80%). mp 188–190 °C (decomp). IR (KBr, cm^{-1}): ν_{max} 3210 (NH broad), 1716 (C=O), 1651 (C=O), 1563, 1520, 1417. ^1H NMR (250 MHz, $CDCl_3$): δ 1.23 (t, 3H, $^3J_{HH}$ = 7.1 Hz, CH_3), 3.70 (t, 2H, $^3J_{HH}$ = 4.0 Hz, CH_2), 4.11 (t, 2H, $^3J_{HH}$ = 4.0 Hz, CH_2), 4.20 (q, 2H, $^3J_{HH}$ = 7.1 Hz, CH_2), 7.72–7.85 (m, 5H, 5H), 8.74 (s, 1H, NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.3 (CH_3), 41.0 (CH_2), 45.2 (CH_2), 62.3 (OCH_2), 118.8 (N–CH=C), 120.5 (C), 123.2 (C of Ar), 123.3 (C of Ar), 127.4 (2CH of Ph), 128.9 (2CH of Ph), 130.9 (C), 132.6 (N–CH=C), 158.3 (C=O), 166.1 (C=O). Anal. calcd. for $C_{16}H_{15}N_3O_5$ (329.32) C, 58.36; H, 4.59; N, 12.76%; Found: C, 58.40; H, 4.40; N, 12.52.

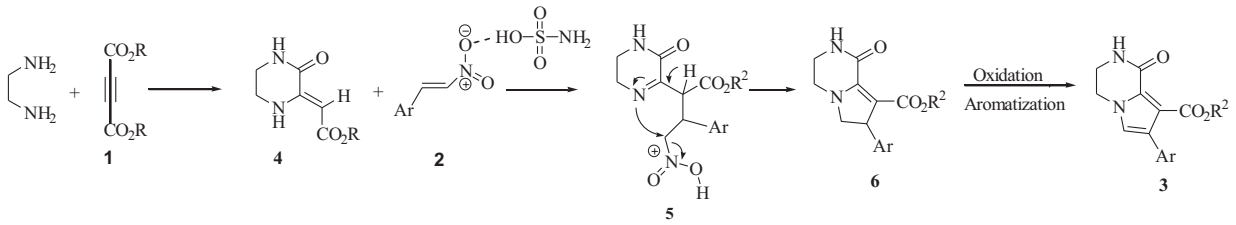
Methyl 7-(4-nitrophenyl)-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-8-carboxylate (***3h***): Gray crystals; 0.25 g (82%). mp 192–194 °C (decomp). IR (KBr, cm^{-1}): ν_{max} 3213 (NH broad), 1714 (C=O), 1650 (C=O), 1561, 1522, 1414. ^1H NMR (250 MHz, $CDCl_3$): δ 3.66 (s, 3H, OCH_3), 3.73 (t, 2H, $^3J_{HH}$ = 4.0 Hz, CH_2), 4.14 (t, 2H, $^3J_{HH}$ = 4.0 Hz, CH_2), 7.75–7.87 (m, 5H, 5H), 8.73 (s, 1H, NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 41.2 (CH_2), 45.1 (CH_2), 52.5 (OCH_3), 118.4 (N–CH=C), 122.5 (C), 123.3 (C of Ar), 124.3 (C of Ar), 127.2 (2CH of Ph), 128.8 (2CH of Ph), 130.6 (C), 132.2 (N–CH=C), 157.3 (C=O), 166.2 (C=O). Anal. calcd. for $C_{15}H_{13}N_3O_5$ (315.29) C, 57.14; H, 4.16; N, 13.33%; Found: C, 57.32; H, 4.10; N, 13.22.

3. Results and discussion

The reaction of ethylenediamine and acetylenic esters **1** with nitrostyrene derivatives **2** in the presence of 20 mol% of SA proceeded in CH_3CN at reflux condition, and was finished after 24 h. Any product other than **3** could not be detected by NMR spectroscopy. Satisfactorily, the reactions displayed high functional group tolerance and afforded the corresponding pyrazines with great efficiency (Table 1). The structure of **3a–3h** was determined

Table 1
Substituted pyrrolo[1,2-*a*]pyrazines.

Compounds	R	R′	Yield (%)
3a	CH_3	C_6H_5	88
3b	CH_3CH_2	*p*-CH_3–C_6H_4	90
3c	CH_3	*p*-CH_3–C_6H_4	95
3d	CH_3CH_2	*p*-Cl–C_6H_4	92
3e	CH_3	*p*-Cl–C_6H_4	90
3f	CH_3CH_2	C_6H_5	87
3g	CH_3	*p*-NO_2–C_6H_4	82
3h	CH_3CH_2	*p*-NO_2–C_6H_4	80



Scheme 2. Possible mechanism for the synthesis of pyrrolo[1,2-*a*]pyrazines derivatives **3a–h**.

on the basis of its elemental analyses, ^{1}H and ^{13}C NMR and IR spectroscopic data. The ^{1}H NMR spectrum of **3a** exhibited two singlets identified as methoxy (δ 3.69) and NH (δ 8.28) protons along with two CH_2 triplets (δ 3.44 and 3.51, J = 3.5 Hz). The phenyl moiety exhibited characteristic signals in the aromatic region of the spectrum. The IR spectrum of **3a** displayed characteristic amide carbonyl, ester carbonyl and N–H vibrations at 1655, 1712, and 3215 cm^{-1}, respectively. The ^{1}H decoupled ^{13}C NMR spectrum of **3a** showed 13 distinct resonances that confirm the proposed structure.

Although the mechanistic details of the reaction are not known, a plausible rationalization may be advanced to explain the product formation (Scheme 2). On the basis of well-established chemistry of amines and DMAD [14] reaction between ethylenediamine and dialkyl acetylenedicarboxylate affords dihydroquinoxaline **4**. Compound **4** possesses enamine character and thus readily reacts with β-nitrostyrene which is activated by SA to generate the intermediate **5**. The subsequent cyclization of intermediate **5** followed by the elimination of the nitro group leads to pyrrole precursor **6**. The elimination of H_2 from the **6** results in pyrrolo[1,2-*a*]pyrazines **3**.

4. Conclusion

In summary, the reaction of ethylenediamine, acetylenic esters and nitrostyrenes in the presence of SA as catalyst provides a simple one-pot synthesis of pyrrolo[1,2-*a*]pyrazines of potential synthetic and pharmaceutical interest. The method carries present the advantage of being performed under the one-pot multicomponent conditions, and requiring no modification of the educts. The simplicity of the present procedure makes it an interesting alternative to other approaches.

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